Journal of Endocrinological Investigation (2020) 43:595–600
https://doi.org/10.1007/s40618-019-01144-0

ORIGINAL ARTICLE

"Block-and-replace" treatment in Graves' disease: experience in a cohort of pediatric patients

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Received: 7 June 2019 / Accepted: 19 October 2019 / Published online: 12 November 2019

Abstract

Purpose The "block-and-replace" (BR) method involves the use of a high dose of antithyroid drugs (ATD) with levothyroxine (L-T4). Its use in the management of Graves' disease (GD) is still debated mainly because the frequency of side effects of ATD is dose dependent. We retrospectively studied the effect of medium dose of ATD with L-T4 versus monotherapy with ATD in pediatric patients with unstable GD.

Methods 28 pediatric patients with GD with unstable response to ATD were treated with L-T4 and medium dose of ATD. We compared the rate of euthyroidism, hypothyroidism and hyperthyroidism episodes observed during treatment with methimazole alone with those observed during the BR approach. We evaluated the occurrence of side effects and the rate of remission in patients treated with ATD + L-T4 therapy and the efficacy of combination therapy to postpone a definitive treatment (radioiodine and thyroidectomy).

Results Patients showed a better control of thyroid function during the BR therapy, presenting fewer episodes of hyperthyroidism and hypothyroidism. No serious side effects during the BR approach were observed. Only one patient went into remission with the ATD + L-T4 therapy. Fifteen patients required a definitive therapy (4 radioiodine, 11 thyroidectomy). The use of BR method has delayed radioiodine treatment for 4.9 years and surgery for 2.9 years.

Conclusions The BR method does not increase the remission rates. It may be useful to combine L-T4 with a medium dose of methimazole when GD is difficult to manage with methimazole alone. It may represent a therapeutic option to postpone definitive treatments to a suitable age.

Keywords Graves' disease · Children · Hyperthyroidism · Antithyroid drugs · "Block-and-replace" method

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in children, with an incidence of 0.02% (1:5000) [1]. The therapy of autoimmune hyperthyroidism represents a real challenge for the pediatric endocrinologist. Currently, the best therapeutic approach is still a matter of debate, due to the paucity of randomized prospective long-term studies on the ratio of disease remission, and on the frequency of short- and long-term side effects of the different therapeutic options (medical treatment, thyroidectomy, and radionuclide ablation). The first-line therapeutic approach in Europe consists in medical therapy with methimazole. This treatment is used for various lengths of time, ranging from 2 to several years. Long-term remission rate is reported to range between 20 and 30% in peripubertal patients, and it is as low as 15% in prepubertal patients [2–4], lower values compared to those observed in adult patients (40–60%) [5–10].

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Radical treatments (total thyroidectomy or radiometabolic therapy) are generally considered in children with relapse after an appropriate course of medical treatment, a lack of compliance by the patient, or severe antithyroid drug (ATD) toxicity. Removal of the thyroid gland with surgical ablation or radioactive iodine treatment is often not fully accepted by the parents, particularly when the patient is young, because of fears of post-intervention complications [11].

When side effects are not present, medical therapy can be continued for several years to reach a favorable age for definitive interventions [4, 12, 13]. During this time, it is essential to maintain a good control over thyroid function in all patients.

The initial starting dose of methimazole is 0.2–1 mg/kg per day (with a maximum of 30 mg per day) [14], depending on the initial severity of the disease. Clinical response becomes apparent after 2–4 weeks, and after that the dose of the medication is usually reduced to the minimum level that maintains the child in a euthyroid state. This approach has been defined as dose titration (DT) regimen. An alternative method, known as block-and-replace (BR) approach, consists in the simultaneous administration of levothyroxine and high doses of methimazole to block the endogenous synthesis of thyroid hormone, while maintaining a euthyroid state by providing exogenous hormone.

Studies comparing the two different therapeutic regimens have been performed in adult patients and gave conflicting results. The recent American Thyroid Association (ATA) guidelines suggest that the BR regimen should not be used [15]. The current evidence among adults supports the DT regimen since the BR approach involves a higher ATD dose and, therefore, a higher prevalence of adverse effects, with no proven benefit in terms of remission [16]. Nevertheless, Razvi et al. [17] in a meta-analysis on the BR methodology revealed that the doses of ATD used in most of the studies considered were much higher than those recommended in clinical practice. This evidence may have been the reason for a higher frequency of side effects observed with the BR approach.

Several studies in the past few years tried to find scores of prediction of hyperthyroidism relapse. These scores, although still unsatisfactory, are useful in selected cases. Patients presenting scores of relapse or clinical signs of predominant Grave's disease should prompt physician to initiate a personalized treatment [18]. Compliance may also be a particularly difficult issue in adolescent patients, who may find it easier to take one ATD rather than two ATD and levothyroxine. However, the BR approach has the advantage of requiring less frequent monitoring and having a more consistent maintenance of euthyroidism than the approach with ATD alone [17, 19].

So far there are no studies on pediatric patients. We report the results obtained in a group of 28 pediatric patients with GD, who showed an unsatisfactory response to methimazole treatment and were switched to a BR approach.

Subjects and methods

Study design and subjects

This is a retrospective study on hyperthyroid children and adolescents who switched from the DT regimen to the BR approach.

We reviewed the medical records of patients referred to our Department between 1990 and 2015. We diagnosed 166 patients with GD, 28 of whom (24 girls and 4 boys) received BR.

The diagnosis of autoimmune hyperthyroidism has been made in the presence of typical clinical features and by finding elevated free tri-iodothyronine (fT3) and free thyroxine (fT4) concentration, thyroid-stimulating hormone (TSH) concentration below the detection limit, anti-TSH receptor antibodies concentration greater than 1 IU/L, and signs of thyroid autoimmune disease at ultrasonography.

All patients were initially treated with methimazole (0.2–0.6 mg/kg/day). However, they showed a poor control of thyroid function with ATD alone (wide fluctuations of hormones concentration following minimal changes of methimazole dose, elevated TSH and fT3 concentration with reduced fT4, or reduced TSH and fT4 values with elevated fT3). Hence, they were switched to a treatment regimen that included levothyroxine at an average dose of 1.12 µg/kg/day (ranging from 0.3 to 2.1 µg/kg/day) and methimazole at a medium dose (on average 0.3 mg/kg/day, ranging from 0.075 to 0.4 mg/kg/day).

We evaluated the thyroid function of all 28 patients during the two treatment regimens, by grouping the subject in euthyroid, hypothyroid, and hyperthyroid according to their biochemical results. We also evaluated the cases of major relapse (inhibited TSH and fT3 with fT4 above reference) and those of minor relapse (inhibited TSH, fT3 above reference and fT4 within reference range). We also assessed changes of the hyperthyroid goiter through ultrasonography.

Adherence to treatment has been evaluated at each visit by interview; family members and patients have been motivated to pursue a meticulous adherence.

Biochemical and imaging studies

All patients' thyroid function was monitored every 2–4 weeks during the first 6 months of medical treatment. Thyroid function was then monitored every 2–4 months. Whenever medical treatment was interrupted, the biochemical analyses were performed initially every 2–3 weeks to evaluate disease relapse. In case of remission, the monitoring

of the thyroid function was performed every 2–4 months in the first 2 years and every 6–12 months after that.

Blood was drawn after an overnight fast, and serum was separated by centrifugation. Serum samples were stored at − 30 °C until assay. TSH, fT4 and fT3 serum concentrations were measured by immunofluorimetry (for normal values we referred to Ranke's reference range by age) [20].

Nineteen patients underwent ultrasonography of the thyroid gland every 12 months.

Statistical analysis

Continuous variables were described using mean and standard deviation or range (min–max). Comparisons between treatments were performed by *t* test. *P* values were considered significant when lower than 0.05.

Results

In our cohort of 28 patients, the diagnosis of autoimmune hyperthyroidism has been made on average at the age of 9.2 years (ranging from 2.58 to 16.83 years).

All patients were initially treated with methimazole for 1.5 years (ranging from 1 month to 7 years). The BR approach has been initiated at an average age of 10.7 years (4.67–15.33 years). At the time of the present study the patients have been receiving the double treatment for 2.85 years (ranging from 5 months to 7 years).

All patients but one had a good compliance. After strong motivation, the compliance of the patient substantially improved during follow-up.

We compared the rate of euthyroidism, hypothyroidism and hyperthyroidism episodes observed during treatment with methimazole alone with those observed during the BR approach. Euthyroid state was present in 47.1 ± 30.9% of cases during methimazole treatment and in the 87.4 ± 18.6% of cases during the BR approach ($P < 0.001$). Episodes of hypothyroidism were recorded in 27.8 ± 27.6% of cases during treatment with methimazole alone, and in 6.8 ± 9.0% of cases of double therapy ($P = 0.001$). Major hyperthyroidism episodes were detected in 14.1 ± 12.7% of cases during treatment with methimazole, and in 1.8 ± 4.1% of cases during double treatment ($P < 0.001$). Finally, minor episodes of hyperthyroidism were present in 11.1 ± 17.0% of cases during methimazole treatment and in 3.6 ± 10.8% of cases during the BR approach.

We observed an increased size of the thyroid gland in nine patients during the double therapy treatment period. The size of the gland was reduced in eight patients, while it was unchanged in the remaining patients.

Only one patient (4%) developed an adverse reaction during the double therapy: we documented a persistent leucopenia with moderate neutropenia (WBC 2200 mm^3, neutrophils 880 mm^3) in the absence of symptoms and documented recurrent infections.

All patients had an adequate growth during the follow-up: we did not record changes of growth velocity in patients receiving two drugs compared to those on monotherapy.

Only one patient (4%) has achieved disease remission after treatment with levothyroxine and methimazole.

Fifteen patients (60%) underwent a definitive treatment, with the development of permanent hypothyroidism: 11 underwent total thyroidectomy, and 4 received a radiometabolic therapy with I-131. The choice of thyroidectomy has been guided by the young age in six patients (< 12 years), by the presence of a goiter in four patients, and by a personal decision in one case. On the other hand, the choice of the use of radioiodine has been driven by the decision of the patients and their families, in the absence of active severe ophthalmopathy. One patient underwent radioactive iodine treatment at the age of 9.5 years due to the poor control of the disease with medical treatment and to the presence of cardiopathy contraindicating surgical intervention. The therapy with levothyroxine and methimazole helped postponing surgical removal of the thyroid gland by 2.9 years (Table 1), while the definitive treatment was postponed by 4.9 years in the four patients who underwent radiometabolic therapy (Table 2). The 13 patients who did not undergo definitive treatment (11 girls, 2 boys) had age at diagnosis ranging from 2.58 to 16.83 years, and received BR treatment for 5–60 months. The decision for definitive treatment was based on several factors, including the age of the patient, his/her ability to understand the consequences of the intervention, and the full knowledge of the parents regarding the need for a replacement therapy.

Discussion

Treatment of GD is still the subject of ample debate. The three therapeutic options available to date (medical treatment with methimazole, surgery, and I-131 radiometabolic treatment) are far from ideal, and they all bear important risks and side effects.

Currently, in Europe, medical treatment is the preferred option in pediatric patients, despite the difficult control of thyroid function, the known side effects, and the low probability of remission.

It is widely accepted that the remission of GD in patients treated with ATD is linked to the restoration of euthyroidism, rather than to the immunosuppressive effects of the drugs. Hyperthyroidism has been shown to aggravate autoimmune problems, and autoimmunity leads to the generation of more TSH receptor antibodies and a worsening of hyperthyroidism. Once this cycle has been broken by medical treatment

Table 1 Age at diagnosis, at the beginning and at discontinuation of treatment with methimazole + L-thyroxine, and at thyroidectomy in the group of the hyperthyroid patients who underwent surgical removal of the thyroid gland

Patient	Age at diagnosis (years)	Age at the beginning of BR approach (years)	Age at the end of BR approach (years)	Age at thyroidectomy (years)
1	8.50	9.0	11.2	11.5
2	3.7	4.6	5.0	6.0
3	12.1	12.5	13.4	13.8
4	9.2	9.6	16.8	17.0
5	8.3	8.9	10.7	11.6
6	5.5	8.3	14.7	15.4
7	9.2	9.5	9.9	9.9
8	5.2	7.5	8.5	10.0
9	8.5	8.6	11.5	11.5
10	10.8	11.6	12.2	14.0
11	10.9	14.6	16.2	16.2

BR block-and-replace approach

Table 2 Age at diagnosis, at the beginning and at discontinuation of treatment with methimazole + L-thyroxine, and at RAI in the group of the hyperthyroid patients who underwent ablation of the thyroid gland by radiometabolic therapy with I-131

Patient	Age at diagnosis (years)	Age at the beginning of BR approach (years)	Age at the end of BR approach (years)	Age at RAI (years)
1	3.5	6.2	12.5	13.5
2	8.1	15.1	19.0	19.0
3	11.5	15.3	17.5	19.6
4	4.5	5.5	9.4	9.5

BR block-and-replace approach, *RAI* = radioactive iodine

restoring the patient's euthyroid state, it is possible to reach a gradual remission of the disease [21, 22]. The combined use of methimazole and levothyroxine to block the endogenous synthesis of thyroid hormone, and at the same time ensuring an euthyroid state, has given conflicting results to date in terms of probability of disease remission [23, 24] and side effects due to the high dose of methimazole utilized [11]. However, the BR approach has the advantage of requiring less frequent monitoring and of more consistent maintenance of euthyroidism than the approach with ATD alone [25].

Our data are in contrast with the results of some studies performed in adult patients, which demonstrated that the BR approach increased the number of disease remissions [23, 24, 26]. Nevertheless, our study showed that in some cases, the use of the dual therapy is more effective than monotherapy with methimazole alone in reducing the rate of hyperthyroidism relapse, or episodes of hypothyroidism, thus, leading to a more stable thyroid function. This, in turn, reduces the need for biochemical and clinical assessments. Furthermore, the improved control of the thyroid function ensures a better well-being for the patient and allows to program surgery or radiotherapy at a more appropriate age. Definitive treatment performed at younger ages has two main drawbacks: technical issues and the psychological problems of the patients and the family related to the invasive procedure.

The other important aspect of our study is related to the safety of the BR approach. The retrospective analysis of our data revealed that medium dose of methimazole (0.3 mg/kg/day) is sufficient to block the endogenous production of thyroid hormone, and it does not lead to increased side effects. Agranulocytosis is a rare but serious side effect of antithyroid treatment. Most of the studies recommend a regular monitoring of white blood cell (WBC) and granulocyte counts during the first 3 months of treatment [27]. However, overdependence on periodic WBC and granulocyte counts should not be encouraged.

Compliance may be particularly difficult in adolescent patients, who may find it easier to take one drug (ATD) rather than two (ATD and levothyroxine). Immediately after the diagnosis of GD, both the parents and the patients should be clearly informed about the clinical outcome and the therapeutic options. An educational program should be set immediately to increase the awareness about the advantages of the therapy and to enforce compliance to treatment.

This study is limited by its retrospective nature and, in particular, by the small number of patients. Prospective trials with more patients need to be conducted to confirm our findings.

A strength of the study is that it is the first study on pediatric patients treated with the BR approach, after an initial unsuccessful phase of medical treatment with methimazole.

Based on the results of our study, we can conclude that the BR approach does not increase the number of disease remissions. It may represent a therapeutic chance to postpone surgical or radiotherapy treatment to a suitable age. The risk of major side effects does not seem to be higher compared to monotherapy with methimazole: it may be

useful to combine levothyroxine with a medium dose of methimazole (and to avoid high doses) when the medical treatment with methimazole alone is not able to guarantee a stable thyroid control.

Funding This study is an academic investigation with no external funding.

Compliance with ethical standards

Conflict of interest All authors do not have conflicts of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional regulations and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from parents or legal guardians of all patients.

References

1. Lavard L, Ranløv I, Perrild H, Andersen O, Jacobsen BB (1994) Incidence of juvenile thyrotoxicosis in Denmark, 1982–1988. A nationwide study. Eur J Endocrinol. 130:565–568. https://doi.org/10.1530/eje.0.1300565
2. Glaser NS, Styne DM, Organization of Pediatric Endocrinologists of Northern California Collaborative Graves' Disease Study Group (2008) Predicting the likelihood of remission in children with Graves' disease: a prospective, multicenter study. Pediatrics 121:e481–e488. https://doi.org/10.1542/peds.2007-1535
3. Shulman DI, Muhar I, Jorgensen EV, Diamond FB, Bercu BB, Root AW (1997) Autoimmune hyperthyroidism in prepubertal children and adolescents: comparison of clinical and biochemical features at diagnosis and responses to medical therapy. Thyroid. 7:755–760. https://doi.org/10.1089/thy.1997.7.755
4. Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P, Léger J, French Childhood Graves' Disease Study Group (2008) Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. J Clin Endocrinol Metab 93:3817–3826. https://doi.org/10.1210/jc.2008-0842
5. Lazar L, Kalter-Leibovici O, Pertzelan A, Weintrob N, Josefsberg Z, Phillip M (2000) Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients. J Clin Endocrinol Metab 85:3678–3682. https://doi.org/10.1210/jcem.85.10.6922
6. Weetman AP (2006) Graves' hyperthyroidism: how long should antithyroid drug therapy be continued to achieve remission? Nat Clin Pract Endocrinol Metab 2:2–3. https://doi.org/10.1038/ncpendmet0068
7. Boiko J, Léger J, Raux-Demay MC, Cabrol S, Le Bouc Y, Czernichow P (1998) Basedow disease in children: clinical and evolutive aspects. Arch Pediatr 5:722–730. https://doi.org/10.1016/S0929-693X(98)80052-3
8. Glaser NS, Styne DM (1997) Predictors of early remission of hyperthyroidism in children. J Clin Endocrinol Metab 82:1719–1726. https://doi.org/10.1210/jcem.82.6.3986
9. Zimmerman D, Gan-Gaisano M (1990) Hyperthyroidism in children and adolescents. Pediatr Clin North Am 37:1273–1295. https://doi.org/10.1016/S0031-3955(16)37011-0
10. Hamburger JI (1985) Management of hyperthyroidism in children and adolescents. J Clin Endocrinol Metab 60:1019–1024. https://doi.org/10.1210/jcem-60-5-1019
11. Rivkees SA (2016) Controversies in the management of Grave's disease in children. J Endocrinol Invest 39:1247–1257. https://doi.org/10.1007/s40618-016-0177-x
12. Léger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C, French Childhood Graves' Disease Study Group (2012) Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. J Clin Endocrinol Metab 97:110–119. https://doi.org/10.1210/jc.2011-1944
13. Léger J, Carel JC (2017) Management of endocrine disease: arguments for the prolonged use of antithyroid drugs in children with Graves' disease. Eur J Endocrinol 177:R59–R67. https://doi.org/10.1530/EJE-16-0938
14. Kaguelidou F, Carel JC, Léger J (2009) Graves' disease in childhood: advances in management with antithyroid drug therapy. Horm Res 71:310–317. https://doi.org/10.1159/000223414
15. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN et al (2016) 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 26:1343–1421. https://doi.org/10.1089/thy.2016.0229
16. Abraham P, Avenell A, Park CM et al (2005) A systematic review of drug therapy for Graves' hyperthyroidism. Eur J Endocrinol 153:489–498. https://doi.org/10.1530/eje.1.01993
17. Razvi S, Vaidya B, Perros P, Pearce SH (2006) What is the evidence behind the evidence-base? The premature death of block-replace antithyroid drug regimens for Graves' disease. Eur J Endocrinol 154:783–786. https://doi.org/10.1530/eje.1.02169
18. Masiello E, Veronesi G, Gallo D, Premoli P, Bianconi E, Rosetti S, Cusini C, Sabatino J, Ippolito S, Piantanida E, Tanda ML, Chiovato L, Wiersinga Bartalena L (2018) Antithyroid drug treatment for Grave's disease: baseline predictive models of relapse after treatment for a patient-tailored management. J Endocrinol Invest 41:1425–1432. https://doi.org/10.1007/s40618-018-0918-9
19. Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS (2010) Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD003420.pub4
20. Ranke MB (2003) Diagnostics of endocrine function in children and adolescents. In: Basel, Karger, 2003, pp 93–106. Diagnostic Tests of Thyroid Function in Children and Adolescents
21. Leger J, Kaguelidou F, Alberti C, Carel JC (2014) Graves' disease in children. Best Pract Res Clin Endocrinol Metab 28:233–243. https://doi.org/10.1016/j.beem.2013.08.008
22. Laurberg P (2006) Remission of Graves' disease during antithyroid drug therapy. Time to reconsider the mechanism? Eur J Endocrinol 155:783–786. https://doi.org/10.1530/eje.1.02295
23. Romaldini JH, Bromberg N, Werner RS, Tanaka LM, Rodrigues HF, Werner MC, Farah CS, Reis LC (1983) Comparison of effects of high and low dosage regimens of antithyroid drugs in the management of Graves' hyperthyroidism. J Clin Endocrinol Metab 57:563–570. https://doi.org/10.1210/jcem-57-3-563
24. Kuo SW, Huang WS, Hu CA, Liao WK, Fung TC, Wu SY (1994) Effect of thyroxine administration on serum thyrotropin receptor antibody and thyroglobulin levels in patients with Graves' hyperthyroidism during antithyroid drug therapy. Eur J Endocrinol 131:125–130
25. Cheetham TD, Hughes IA, Barnes ND et al (1998) Treatment of hyperthyroidism in young people. Arch Dis Child 78:207–209. https://doi.org/10.1136/adc.78.3.207
26. Hashizume K, Ichikawa K, Sakurai A, Suzuki S, Takeda T, Kobayashi M, Miyamoto T, Arai M, Nagasawa T (1991) Administration of thyroxine in treated Graves' disease. Effects on the level

of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. N Engl J Med 324:947–953. https://doi.org/10.1056/NEJM199104043241403

27. He Y, Li J, Zheng J, Khan Z, Qiang W, Gao F, Zhao Y, Shi B (2017) Emphasis on the early diagnosis of antithyroid drug-induced agranulocytosis: retrospective analysis over 16 years at one Chinese center. J Endocrinol Invest 40:733–740. https://doi.org/10.1007/s4618-017-0626-x