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Treatment for Graves' Disease and its Recurrence

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INTRODUCTION

The most common cause of hyperthyroidism worldwide is Graves' disease (GD). Therapeutic options for GD include anti thyroid drugs (ATD), radioactive iodine, and thyroidectomy. ATD treatment is generally well accepted by patients because it normalize thyroid function in a short time, rarely causing hypothyroidism, and ameliorating immune disorder while avoiding radiation exposure and invasive procedures. However, the relapse rate is a major concern for ATD treatment, the rate of relapse depends on the factors like clinical characteristics, treatment strategies, and genetic and environmental factors. Of these influencing factors, some are modifiable but some are non modifiable. The recurrence risk can be reduced by adjusting the modifiable factors as much as possible. The titration regimen for 12–18 months is the optimal strategy of ATD. Levothyroxine administration after successful ATD treatment was not recommended. The addition of immunosuppressive drugs might be helpful to decrease the recurrence rate of GD patients after ATD withdrawal, whereas further studies are needed to address the safety and efficacy.

Drugs

The commonly used ATD include carbimazole and propylthiouracil [1]. Carbimazole exerts its pharmacological effect by converting to methimazole, so it has similar efficacy and features as carbimazole. Previous studies showed that carbimazole had a better efficacy and restored the euthyroid state much faster than propylthiouracil, but the recurrence rate after withdrawal was comparable between the two drugs in GD patients. The side effects of ATD is common (13%) but generally mild, including rash, pruritis, metallic taste, arthralgia, and liver damage [2]. A meta-analysis of studies showed that rash was more common with carbimazole treatment, whereas the predominant side effects of propylthiouracil was hepatic involvement [2]. ATD treatment also had some major side effects, including agranulocytosis and severe hepatotoxicity, which are life threatening but rare (<0.5%) [2]. Carbimazole has longer half-life and duration of action and fewer major side effects as compared to propylthiouracil[2,4]. Thus, carbimazole is recommended as the preferred drug for GD patients by ATA guidelines except for pregnant women during the first trimester [2,4].

There are two regimens of ATD: titration-block and block-replace regimens. The titration-block regimen means that the ATD dose is titrated from the initial higher dose to the lowest dose for maintaining a euthyroid state, and the block-replace regimen is initiated with a standard dose of ATD and the addition of levothyroxine. The initial dose of ATD depends on the severity of hyperthyroidism. Patients with mild hyperthyroidism begin with 15–30 mg daily of carbimazole, while 20–40 mg daily is given to patients with severe hyperthyroidism. A recent meta-analysis showed that the two regimens had similar recurrence rates, but the block-replace regimens caused relatively more side effects [16].

Just as important, the treatment duration of ATD also impacts the recurrence risk of GD patients [7]. Recently, increasing evidence has demonstrated that ATD treatment for 12–18 months leads to a better prognosis than the 6-month treatment [7, 12]. The results from a recent meta-analysis showed that the 12-month titration regimen has a lower recurrence rate than the 6-month regimen, but extending treatment beyond 18 months failed to provide more benefits [19]. In addition, considering the high recurrence rate after drug withdrawal, some studies even advocated a continuous treatment with low-dose ATD for GD patients[13]. They proposed that long-term maintenance of low-dose ATD had a persistent effect on preventing recurrence[13]. However, because of the intermittent blood check and higher medical costs during long-term ATD maintenance, the titration regimen for 12–18 months is still considered as the optimal strategy of ATD.

Levothyroxine Administration

Because increased TSH levels have been incriminated for promoting the production of TRAb, some studies have been conducted to evaluate whether levothyroxine administration after successful ATD treatment could decrease the recurrence risk of hyperthyroidism in GD patients [14] Nevertheless, these studies demonstrated that levothyroxine does not prevent recurrence of hyperthyroid-ism in GD patients after successful ATD treatment [14]. Some studies even observed that levothyroxine administration after successful ATD treatment was associated with increased recurrence risk of GD patients. Thus, levothyroxine administration after successful ATD treatment was not recommended.

Use of Immunosuppressive Drugs

Considering the autoimmune nature of GD, several studies have attempted to evaluate the effect of additional use of immunosuppressive drugs. The immunosuppressive drugs for GD patients mainly included corticosteroid and non corticosteroid drugs [16] A recent meta-analysis demonstrated a strong reduction of the recurrence risk when immunosuppressive drugs were added to standard ATD treatment in GD patients. In this meta-analysis, the overall recurrence rate in GD patients receiving the addition of immunosupp-ressive drugs was 23.5%, which was significantly lower than 59.1% in GD patients only treated with ATD [18]. Therefore, the addition of immunosup-pressive drugs might be helpful to decrease the recurrence rate of GD patients after ATD withdrawal, whereas there are still some disadvantages to mention. First, studies addressing immunosuppressive treatment for GD are always small, single-center, and with low to moderate quality and high risk of bias [16,17]. Second, the side effects of immunosuppressive drugs should have great importance [30]. The administration mode of immunosuppressive drug included oral and local administrations. How-ever, the side effects should not be disregarded, no matter the mode [30]. The side effects of corticosteroids include bone abnormalities, metabolic disturbances, and muscle wasting, and rituximab was associated with leucopenia, rash, minor infections, chills, and fever [18]. Therefore, further large-scale randomized controlled trials are needed to address the safety, efficacy, optimal timing, and duration of immunosuppressive drugs in GD patients.

Factors for the Recurrence

General

The incidence of GD gradually increases with age and then remains stable after the age of 30 . It is generally accepted that younger GD patients have more severe immune disorders. Previous studies showed that younger GD patients have a relatively poor response to ATD and often have a poor prognosis and higher recurrence risk [5]. A study found that GD patients younger than 40 years had a higher recurrence rate than older patients.

Females have a higher incidence of GD than males [19]. The reason for a different incidence in gender is unclear and might be associated with varying sex hormones. Estrogens influenced B-cell function and further regulated the immune system. In GD patients, the increased estradiol level is related to the positivity of TRAb. Although the incidence of GD is higher in women, male GD patients have a higher risk of recurrence after ATD withdrawal [6] There are some possible explanations for the higher recurrence risk of male GD patients. The higher risk of recurrence in male GD patients might be associated with bigger goiter size and genetic background. However, this is still a conflicting issue since other studies have inconsistent results [20].

Several studies showed that smokers have a higher recurrence risk than nonsmokers in GD patients after ATD withdrawal. Meanwhile, quitting smoking has also been demonstrated to protect against recurrence in GD patients [20]. A study showed that smokers had significant higher TRAb levels than nonsmokers at 4 weeks after ATD withdrawal[21]. Therefore, smoking might promote immune disorder and elevate TRAb levels, contributing to the increased recurrence risk. Because there were some inconsistent results, the association between smoking and the recurrence rate still remains uncertain [8].

Biochemical Parameter

The severity of GD is associated with the recurrence risk in GD patients treated with ATD [8,22]. The biochemical parameters partially represent the severity of GD [8, 22]. The key feature in untreated GD is the significant increase in the serum triiodo-thyronine (T3) level, which is caused by the elevated activity of intrathyroidal type 1 deiodinase [1]. Previous studies showed that the serum T3 levels and free T3 (FT3)/free thyroxin (FT4) ratios at the onset of GD were independent factors for predicting outcomes of ATD treatment in GD patients [22]. Patients with mild hyperthyroidism can achieve remission after just treatment with beta blockers [48]. However, patients with higher serum T3 levels and FT3/FT4 ratios have a relatively higher recurrence risk, so they often need a higher initial dose and longer treatment duration. Furthermore, a high T3/T4 ratio during ATD withdrawal also predicts a higher recurrence risk in GD patients [4]. The therapy duration should be prolonged in patients with a high T3/T4 ratio even after 12–18 months of ATD treatment.

In addition, the serum TSH level also should get more attention. As is known, the thyroid hormone can inhibit TSH via a negative feedback mechanism. In some GD patients, the TSH level still sustained suppression and failed to return to a normal range with the normalization of thyroid hormone after ATD treatment. Previous studies have demonstrated that TSH suppression after drug withdrawal was a predictor for the recurrence of GD [8]. These studies suggested that GD patients with delayed TSH restoration should receive prolonged ATD treatment until their TSH levels reach the normal range.

Immune Parameters. As mentioned before, GD results from the over activated TSH receptor in the thyroid follicular cells by TRAb [1]. TRAb is positive in about 95% of patients with newly diagnosed GD, and the higher TRAb levels hint a severe immune disorder [1, 5, 23,24]. In recent years, with increased accuracy of assay, TRAb has been supported as a useful predictive factor for the outcome of ATD treatment by many studies [23, 24]. Patients with higher TRAb levels at the time of GD diagnosis have significantly increased recurrence risk, while TRAb-negative patients

often have a better prognosis and are prone to long-term remission. Furthermore, a shift from positive to negative in TRAb may imply the alleviated immune disorder following ATD treatment in GD patients. The TRAb level at ATD withdrawal was also associated with the prognosis of GD patients. The recurrence risk was higher in TRAb-positive GD patients at the time of drug withdrawal. In addition, TRAb can be distinguished from the stimulating (TSAb) and blocking (TBAb) properties by using new assay techniques [53]. Antibodies of GD patients are predominantly TSAb [1]. Recently, TSAb has been demonstrated to have a superior predictive value for recurrence risk than TRAb in GD patients treated with ATD.

GD and Hashimoto's thyroiditis are the two main autoimmune thyroid diseases [22]. GD is possibly concomitant with Hashimoto's thyroiditis [27]. GD patients with Hashimoto's thyroiditis tend to be in remission after ATD treatment due to the progressive damage induced by Hashimoto's thyroiditis. The positivity of peroxidase auto antibodies (TPOAb) and/or thyroglobulin antibody (TgAb) is the main feature of Hashimoto's thyroiditis, the association between the positivity of TgAb/TPOAb and the recurrence risk in GD patients.

Clinical Symptoms

Large goiter size is a main clinical manifestation of GD patients [5,8]. Goiter size is a major predictor of a higher recurrence risk in GD patients after ATD withdrawal [5, 8]. GD patients with significantly decreased goiter sizes after ATD treatment also tend to have higher remission rates. These studies suggested that enlarged goiter size at the time of GD diagnosis and drug withdrawal is associated with a higher recurrence risk.

Graves' orbitopathy is present in around 30% of patients at the time of diagnosis of GD [20, 28]. The presence of Graves' orbitopathy often suggested a worse disorder of the immune system. Previous studies have shown that patients with Graves' orbitopathy have a higher recurrence risk of GD after ATD withdrawal. A study by Eckstein et al. even found that the remission rate of GD patients with severe Graves' orbitopathy was just 7% [29]. Even with the higher recurrence rate, ATD treatment is still a preferred therapeutic option for GD patients with Graves' orbitopathy due to a better outcome for Graves' orbitopathy, which might be associated with the stable euthyroid status and decreased levels of TRAb and inflammatory markers. Recent studies have shown that a prolonged low dose of ATD treatment contributed to a better outcome in GD patients with Graves' orbitopathy.

Genetic factors like cytotoxic T-lymphocyte-associated factor 4 (CTLA4) rs231775 and rs231779 polymorphisms were associated with recurrence in GD patients after ATD withdrawal in Asians. GD, the recurrence risk after ATD withdrawal is related to the polymorphisms of HLA DQA2, HLA DRB1* 03, and HLA DQB1* 02 in some population [5]. The HLA region contains some immune response genes and these HLA polymorphisms might influence the outcome of GD patients by regulating the immune system.

Environmental Factors

In the individuals with the predisposed gene [30]. The association between stress and the recurrence of GD patients after ATD treatment was supported by most studies. It is worth mentioning that psychosocial stress is an important part of a stressful event. Previous studies showed that GD patients with psychiatric disorders such as depression and hypochondriasis had a higher recurrence risk than GD patients without such disorders. Thus, reducing stress as much as possible is an important way to improve the prognosis of GD patients with ATD treatment.

Iodine is a major substrate for the synthesis of thyroid hormone [31]. In thyrocytes, increased iodine content promoted ATD degradation and reduced ATD uptake. The administration of pharmacological doses of iodine caused the onset of hyperthyroidism in euthyroid GD patients after ATD withdrawal. The recurrence rate in iodine

sufficient regions is not higher than that in iodine-deficient regions in GD patients after ATD withdrawal. In a recent Korean study, excessive iodine did not influence the outcomes of GD. The study suggested that dietary iodine restriction might not be necessary for GD patients after ATD withdrawal. In addition, a previous study showed that a dietary change from a low-iodine to a high-iodine intake increased the recurrence rate in GD patients after ATD treatment [32]. Thus, these results might suggest that only a sudden increase in iodine intake induces the recurrence of GD. Further large-scale intervention studies are needed to evaluate the effect of iodine uptake on the recurrence risk in GD patients after ATD withdrawal.

In addition, baseline vitamin D and selenium levels might impact the outcome of GD patients after ATD treatment. Vitamin D has been demonstrated as an immune modulator [33]. ATD treatment caused a greater decline in TRAb in GD patients with normal vitamin D levels compared to that in GD patients with decreased vitamin D levels . Moreover, a decreased baseline vitamin D level was associated with greater thyroid goiter in female patients with newly onset GD . Selenium is another component element of thyroid function. As a basic component of glutathione peroxidase and iodothyronine selenodeiodinase, selenium deficiency might impact the conversion of T4 to T3 and the production of free radicals. The association between inadequate selenium supply and GD has been found by many studies. Furthermore, decreased serum selenium levels were also related to severe immune disorders and the incidence of Graves' orbitopathy. High serum selenium levels were also shown to be associated with higher remission rates in GD patients. Recently, more studies have found that selenium supplementation can enhance biochemical restoration of hyperthyroidism and improve the remission rate of GD patients.

Treatment for Recurrence of GD

The high recurrence rate is a major drawback of ATD therapy, and patients with recurrent GD often have a much higher recurrence risk than average. Most clinicians will recommend radioactive iodine or thyroidectomy for recurrent GD patients [34]. However, some recent studies have found that compared with radioactive iodine or thyroidectomy, the prolonged low dose ATD treatment retained a stable euthyroid state while minimizing the risk of side effects [35]. A recent prospective clinical study showed that ATD treatment also reached a higher remission rate in recurrent GD patients, and a much lower discontinuation drug dose of carbimazole (2.5 mg qod) increased the rate of permanent remission. In a recent study, during a long-term follow-up (up to 7 years), prolonged low-dose treatment was safe and effective and with fewer complications and less expense in recurrent GD patients. It also contributes to a better outcome of Graves' orbitopathy and a lower frequency of thyroid dysfunction than radioactive iodine. Thus, prolonged low-dose carbimazole treatment might be a good alternative for recurrent GD patients who resist radioactive iodine or thyroidectomy.

Conclusions

Recurrence in GD patients with ATD treatment is associated with multiple influential factors such as clinical characteristics, treatment strategies, and genetic and environmental factors. Of these influencing factors, some are modifiable but some are non modifiable. The recurrence risk can be reduced by adjusting the modifiable factors as much as possible. If the recurrence evaluation based on the non modifiable factors strongly suggests a high risk of recurrence, a definitive treatment such as radioactive iodine or thyroidectomy is considered as an appropriate therapeutic approach. However, prolonged low-dose carbimazole treatment might be a good alternative for GD patients with high recurrence risk due to its safety and efficacy. The addition of immune suppressive drugs might be helpful to

decrease the recurrence rate of GD patients after ATD withdrawal, whereas further studies are needed to address the safety and efficacy. Further large-scale prospective studies are also needed to observe whether the administration of vitamin D and selenium can bring benefit.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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