

Study Protocol

A Prospective Clinical Follow-up Study of Drug Treatment in
Patients with Graves' Disease

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I. Research Content

Graves' disease (GD) is a common disease in endocrinology department, its prevalence rate is as high as 1.5%. Antithyroid drugs (ATD) are the first choice for GD treatment. However, there are some problems in drug treatment of GD: 1. ATD treatment cycle is long, the rate of loss to follow-up is high, and the recurrence rate is high. Foreign guidelines recommend that ATD treatment should be stopped for about 1.5-2 years. Foreign literature reports that the recurrence rate varies from 10-60% after drug withdrawal. GD recurrence was closely related to race, inclusion criteria, study nature (prospective or retrospective), and thyrotropin receptor antibody (TRAb) titers at discontinuation. 2. ATD treatment may lead to leukopenia and liver function impairment, but when these side effects occur, their severity and which factors are related to them, China still lacks prospective clinical studies with large sample size in this respect.

This study was a prospective follow-up study of newly diagnosed and relapsed Graves' disease patients in the Endocrinology Clinic of the First Affiliated Hospital of China Medical University. The following aspects will be studied: 1. Through the prospective follow-up study of GD patients, we will get the relapse rate and remission rate of GD patients treated with drugs, explore the risk factors of GD patients relapsing after drug treatment, and make GD relapse risk prediction software; 2. To compare the effects of high dose and low dose methimazole on the remission rate, liver side effects, leukopenia and other adverse drug reactions, and to summarize the incidence and risk factors of liver side effects, leukopenia and other adverse drug reactions caused by drug treatment; 3. To investigate the sensitivity and specificity of TRAb in the diagnosis of GD in China and its role in predicting recurrence; 4. After taking ATD, the serum alkaline phosphatase of GD patients will increase first and then decrease. This study will focus on analyzing the dynamic changes of this index before and after methimazole treatment, and analyze the relationship between it and thyroid function index.

II. Research objectives

By utilizing the leading position of this discipline in the research field of thyroid science in China, we can accumulate the treatment experience of Graves' disease in China and provide our own experience for the formulation of hyperthyroidism guidelines in China.

III. Research technique

1. Patient inclusion criteria
 - ① Newly diagnosed GD and GD relapses.
 - ② Patients with active infiltrative exophthalmos in GD were excluded.
 - ③ Patients with other autoimmune diseases affecting thyroid function were excluded.
 - ④ Excluding patients with combined malignancies and other serious diseases.
2. GD patients were recruited according to the above inclusion criteria. Follow-up records were established for GD patients identified for enrollment. According to the guidelines, outpatient follow-up is required every month until the patient has normal thyroid function; after the thyroid function is normal, outpatient follow-up is required every 2-3 months.
3. GD patients enrolled were identified and thyroid function, liver function, TRAb and blood routine tests were performed during outpatient follow-up to observe the treatment effect and give medication guidance.
4. To determine the GD patients enrolled, record the laboratory test results at each follow-up visit and enter them into the database established in this study. At each follow-up visit, the GD patients enrolled should collect and retain blood samples and store them frozen at -80°C for subsequent study.
5. To investigate the risk factors of GD relapse and drug-induced side effects, genetic, epigenetic and proteomic studies were performed on preserved blood samples of GD patients.

IV. Statistical analysis plan

Continuous variables were presented as median (25th–75th percentile) or mean±standard deviation and compared using the Mann–Whitney U test or independent sample t-test. Categorical variables were presented as frequency and percentage and compared using the chi-square or Fisher's exact tests. Univariate and multivariate Logistic regression analyses were used to estimate the odds ratio and 95% confidence intervals for potential risk factors for recurrence of hyperthyroidism and adverse reaction under MMI treatment. $P < 0.05$ was considered statistically significant.

V. Experimental Feasibility Analysis

The Department of Endocrinology of the First Affiliated Hospital of China Medical University is in the leading position in the field of thyroid research in China. The outpatient volume of thyroid diseases accounts for about 50% of endocrine diseases. It is fully capable of conducting prospective clinical follow-up observation of Graves' disease. The research direction of the project leader is thyroid diseases, and he has accumulated rich clinical experience in the diagnosis and treatment of thyroid diseases.

VI. Expected experimental results

1. To obtain and analyze the remission rate, recurrence rate and related risk factors of Graves' disease patients.
2. To obtain and analyze the prevalence of side effects and associated risk factors of drug therapy in patients with Graves' disease.
3. To evaluate the sensitivity and specificity of TRAb in the diagnosis of Graves' disease and its role in predicting recurrence.
4. Through the implementation of this project, a standardized management model for GD treatment follow-up has been established. After that, relying on our leading role in the national thyroid field, we will further carry out a national multicenter clinical study of GD.