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Personalised immunomodulating treatments for Graves' disease: fact or fiction?

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Summary

Although Graves' disease has been recognised for more than 100 years, its physiopathological mechanisms are incompletely understood. Treatment strategies today mainly focus on suppression of thyroid hormone production by use of antithyroid drugs or radio-iodine, but neglect the underlying immunological mechanisms. Although Graves' disease is often seen as a prototype for an autoimmune mechanism, it is more likely to be a heterogeneous syndrome showing characteristics of both autoimmunity and immunodeficiency. The interplay of these two mechanisms may well characterise the physiopathology of this disease and its complications. Immunodeficiency may be either genetically determined or secondarily acquired. Various triggering events lead to autoimmunity with stimulation of the thyroid gland resulting in the clinical syndrome of hyperthyroidism. Also, relapse risk differs from patient to patient and can be estimated from clinical parameters incorporated into the Graves' Recurrent Events After Therapy (GREAT) score. Accurate risk stratification may help to distinguish high-risk patients for whom a more definitive treatment approach should be used from others where there is a high probability that the disease will recover with medical treatment alone. Several smaller trials having found positive effects of immunosuppressive drugs on recurrence risk in Graves' disease; therefoore, there is great potential in the use of novel immunomodulating drugs in addition to the currently used antithyroid drugs for the successful treatment of this condition. Further in-depth exploration of susceptibility, triggering factors and immunological mechanisms has the potential to improve treatment of Graves' disease, with more personalised, risk-adapted treatment strategies based on the different physiopathological concepts of this heterogeneous condition.

Key words: Graves' disease, review, aetiology, pathophysiology

Author contributions
TS, AK, BM, and PS initially conceptualised this review. All authors searched the literature and reviewed the references retrieved through the search. TS wrote the first draft of the manuscript and had primary responsibility for final content. All authors read and approved the final manuscript.

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Introduction and aims

Graves' disease was first recognised over 100 years ago as an illness comprising an enlarged and overactive thyroid gland, an accelerated heart rate and ocular abnormalities [1]. Although the precise underlying mechanisms are incompletely understood, an association between Graves' disease and other autoimmune diseases has been demonstrated. The association of Graves' disease with other autoimmune diseases, namely the autoimmune polyendocrine syndromes (APS), makes autoimmune mechanisms resulting from complex interactions between genetic and environmental factors highly likely. One factor that has been elucidated most is the role of thyrotropin-related antibodies (TRAbs). As their formation precedes and inevitably leads to the occurrence of Graves' disease, they seem to represent the final common pathway. Various steps are required before TRAbs become pathogenic. One step is a somatic hypermutation of precursor B cells to recognise the outer membrane porins of *Yersinia enterocolitica*, leading to cross-reactivity to a pathogen and the thyroid stimulating hormone (TSH) receptor [2].
Interestingly, several randomised trials found positive effects of corticosteroids and other immunomodulating drugs on recurrence risk of Graves' disease [3]. Also, several predisposing (risk) factors have been found that help to estimate the probability of successful treatment of this condition [3]. Within this current viewpoint article, we discuss novel immunological mechanisms that may be important for the pathogenesis of Graves' disease and new research into risk prediction and use of immunomodulating drugs, which may have an impact on the treatment of patients in the future [4, 5].

Risk factors for relapse of hyperthyroidism

In iodine sufficient areas, Graves' disease is the most common cause of primary hyperthyroidism, with a prevalence of around 0.5% [6]. In Asia and Europe, Graves' disease is usually treated with antithyroid drugs for 12 to 18 months [6]. However, 40 to 60% of patients suffer a relapse of hyperthyroidism after stopping medical treatment [7, 8]. In these situations, more definitive treatment options, including surgery or radio-iodine, are usually recommended. Different risk factors for relapse after stopping antithyroid drugs have been reported, including younger age, goitre size, smoking, male sex, more severe biochemical disease and high levels of antibodies, among others [6]. In a recent

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systematic review and meta-analysis, we screened 1859 articles and identified 54 relevant studies including 7595 patients that reported risk factors for Graves' disease relapse. Smoking, goitre size, occurrence of endocrine orbitopathy, abnormal biochemistry (free thyroxine [fT4], total triiodothyronine, TRAbs) and various genetic polymorphisms were associated with relapse risk. Other factors, such as age, male gender, and initial total thyroxine levels were not significantly associated with relapse [9]. Quantitative analysis with meta-regression revealed low prognostic accuracy of these factors when used individually. Thus, unless more powerful individual prognostic indicators become available, combination of several risk factors into a risk score is mandatory to better estimate the probability of relapse in an individual patient.

The GREAT score for risk stratification

Recently, a Dutch study group proposed the Graves' Recurrent Events After Therapy (GREAT) score, which groups patients into three risk classes based on various clinical parameters [10]. The score was derived from a prospective study of 178 patients with their first episode of Graves' hyperthyroidism treated with antithyroid drugs. Younger age, larger goiters, higher serum fT4, and higher serum thyrotropin-binding inhibitor immunoglobulin (TBII) were identified as independent risk factors. Smoking, gender, orbitopathy, and thyroperoxidase-antibodies did not show any predictive power. The GREAT score showed moderate discrimination between patients with and without relapse with an area under the curve (AUC) of 0.67 (95% confidence interval [CI] 0.54–0.77). This score was further refined by incorporating genetic information – PTPN22 C/T polymorphism, and human leucocyte antigen (HLA) subtypes DQB1*02, DQA1*05 and DRB1*03 – and called the GREAT+. The greatest benefit of the addition of genotyping was seen in patients with an intermediate risk.

As statistical models usually fit well in their derivation sample, we recently externally validated the GREAT score in a large retrospective analysis from four Swiss endocrine outpatient clinics [11]. Of 741 included patients, 371 relapsed (50.1%) after a mean follow-up of 26 months after initiation antithyroid drug therapy. We found a strong increase in relapse risk with more points in the GREAT score from 33.8% in patients with GREAT class I (0–1 points), 59.4% in class II (2–3 points) with a hazard ratio of 1.79 (95% CI 1.42–2.27, $p<0.001$) and 73.6% in class III (4–6 points). Compared with the initial study, we found a higher relapse rate (50 vs 36%). This difference may be explained by several factors, including selection bias in the original study (the authors excluded a substantial number of patients, 67 of 263), differences in patient's race and initial treatment (thyroid ablative procedures) among others. Based on this external validation, we believe that the GREAT score could become part of a standard assessment before the start of antithyroid drug treatment in patients with Graves' disease. Also, with more immunological exploration of this disease, the score may be refined in the future to improve its accuracy.

Are there benefits of additional immunosuppressive therapy in Graves' disease?

Since their advent in the 1920ies, antithyroid drugs have become the mainstay of medical therapy in Graves' disease [1]. Whereas therapy of other autoimmune diseases has made great progress in the last 60 years since the introduction of glucocorticoids into therapy, little has changed in the field of Graves' disease, albeit the autoimmune nature of the disease was unveiled in 1956 [1].

There have been some attempts to evaluate immunosuppressive drugs in Graves' disease in the past, but they are currently not recommended by international guidelines owing to lack of more conclusive data derived from high quality trials. Recently, a systematic review of trials addressed the question of whether the addition of immunosuppressive drugs to antithyroid drug therapy reduces relapse risk in Graves' disease [3]. Seven trials with 862 participants were included. Data were pooled with use of a random-effects model and a risk ratio for recurrence of 0.55 (95% CI 0.41–0.75) was found for patients receiving immunosuppressive drugs. It is important to recognise that most trials were small with moderate to high risk of bias, mostly old and heterogeneous, and adverse effects were not systematically reported. Nonetheless, results remained consistent in subgroup analyses for trials using corticosteroids and noncorticosteroid drugs and for randomised trials as well as nonrandomised controlled trials. Given the promising findings with a relevant reduction in recurrence risk in Graves' disease when immunosuppressive drugs are added to a antithyroid drug regimen, this approach needs large-scale validation in a high-quality randomised trial before such protocols are used in standard care.

Graves' disease as a primary immunodeficiency disease?

In addition to new research about risk prediction and immunosuppressive treatment options for Graves' disease, there has also been progress in the understanding of the underlying pathophysiology. Relapse rates of hyperthyroidism are higher in the young, which may be explained by genetic susceptibility. Also, monozygotic twins share a concordance of up to 80% [12–14], which supports the hypothesis of genetic susceptibility. We have recently learned from patients with primary immunodeficiency diseases such as common variable immunodeficiency (CVID) or selective IgA deficiency that autoimmune complications may occur later in life. Immunodeficiency thus seems to be entangled with autoimmunity [5]. The Fas(CD95)/Fas-ligand system is an important regulatory mechanism in the control of autoreactive T cells. Binding of the Fas-ligand to its receptor Fas activates apoptosis through activation of intracellular caspases. Like Graves' disease, a primary immunodeficiency disease with a lymphoproliferative syndrome and autoimmunity ensues in cases of Fas-ligand mutations. Interestingly, a cohort of 28 patients with Graves' disease has been described, of whom 24 had impaired T cell apoptosis after Fas binding [15]. Furthermore, there is the question of why thyrocytes in Hashimoto's thyroiditis succumb to apoptosis, whereas those in Graves' disease do not [16]. This might be explained by the fact that intrathyroidal T cells in Graves' disease release apoptosis-inhibiting factors

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such as caspase-8 inhibitor protein and antiapoptotic Bcl proteins [17].

Autoreactive cells occur on a daily basis in every human and need to be tightly controlled. Autoreactive T cells are kept in control by regulatory T cells (Tregs). Essential for the maturation of these Tregs is the transcription factor forkhead box P3 (FOXP3). Mutations in FOXP3 lead to the immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, which is characterised by the loss of Tregs and manifestation of eczema, enteropathy and endocrinopathy (both hypo- and hyperthyroidism) [18, 19].

Although there are only few and small studies, one analysis provided evidence that the number and function of Tregs was significantly reduced in the blood of Graves' disease patients [20]. Interestingly, FOXP3 is located on the X chromosome, which might explain the female predominance in autoimmune diseases [18].

Though many patients do not have symptoms, selective IgA deficiency is the most prevalent form of immunodeficiency worldwide. Many persons develop autoimmune diseases, including Graves' disease, and it is believed that the interplay between IgA and its receptor deactivates certain pathways of the immune system [21]. A handful of studies have reported mostly consistent associations between IgA deficiency and various autoimmune diseases (such as celiac disease, rheumatoid arthritis, type 1 diabetes), including Graves' disease [22]. Interestingly, IgA deficiency does not stem from IgA gene mutations, but is associated with the HLA-haplotype 8.1 (i.e. HLA-A1, B8, DR3, DQ2) [21, 23].

In summary, there is evidence that Graves' disease is a heterogeneous syndrome, with patients showing signs of both autoimmunity and immunodeficiency. More profound exploration of these different mechanisms may help us to better understand individual variations in this disease with consequences for relapse risk and treatment approaches in the future.

Conclusion

Although there has been extensive research into the aetiology of Graves' disease, so far no unifying causative agent has been identified. This might reflect the fine balance between anergy and autoimmunity that challenges our immune system daily. In light of these findings, a multifaceted aetiology is very likely. This puts Graves' disease in line with the concept that autoimmunity and immunodeficiency are not two distinct phenomena, but in fact two sides of the same coin. It can thus be speculated that Graves' disease patients in fact have either a genetically determined or secondarily acquired immunodeficiency. A better understanding of the immunological mechanisms may allow more accurate risk prediction and the identification of more personalised drugs that target specific immunological pathways, thereby opening the door for more risk-adapted and personalised treatment approaches in the future.

Disclosure statement

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References

1 Weetman AP. Grave's disease 1835-2002. Horm Res. 2003;(Suppl 1):114–8. PubMed.

2 Hargreaves CE, Grasso M, Hampe CS, Stenkova A, Atkinson S, Joshua GW, et al. Yersinia enterocolitica provides the link between thyroid-stimulating antibodies and their germline counterparts in Graves' disease. J Immunol. 2013;(11):5373–81. doi: http://dx.doi.org/10.4049/jimmunol.1203412. PubMed.

3 Struja T, Guebelin L, Kutz A, Fehlberg H, Mueller B, Schuetz P. Does Immunosuppressive Therapy Improve Outcomes in Graves' Disease? A Systematic Review and Meta-Analysis. Thyroid. 2016;(5):634–40. doi: http://dx.doi.org/10.1089/thy.2015.0647. PubMed.

4 Allenspach E, Torgerson TR. Autoimmunity and Primary Immunodeficiency Disorders. J Clin Immunol. 2016;(S1, Suppl 1):57–67. doi: http://dx.doi.org/10.1007/s10875-016-0294-1. PubMed.

5 Grimbacher B, Warnatz K, Yong PFK, Korganow A-S, Peter H-H. The crossroads of autoimmunity and immunodeficiency: Lessons from polygenic traits and monogenic defects. J Allergy Clin Immunol. 2016;(1):3–17, quiz 18. doi: http://dx.doi.org/10.1016/j.jaci.2015.11.004. PubMed.

6 Franklyn JA, Boelaert K. Thyrotoxicosis. Lancet. 2012;(9821):1155–66. doi: http://dx.doi.org/10.1016/S0140-6736(11)60782-4. PubMed.

7 Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev. 2010;(1):CD003420. doi: http://dx.doi.org/10.1002/14651858.CD003420.pub4. PubMed.

8 Orgiazzi J. Thyroid autoimmunity. Presse Med. 2012;(12 P 2):e611–25. doi: http://dx.doi.org/10.1016/j.lpm.2012.10.002. PubMed.

9 Struja T, Fehlberg H, Kutz A, Guebelin L, Degen C, Muller B, et al. Can we predict relapse in Graves' disease? Results from a Systematic Review and Meta-analysis. Eur J Endocrinol. 2017;(1):87–97. doi: http://dx.doi.org/10.1530/EJE-16-0725. PubMed.

10 Vos XG, Endert E, Zwinderman AH, Tijssen JGP, Wiersinga WM. Predicting the Risk of Recurrence Before the Start of Antithyroid Drug Therapy in Patients With Graves' Hyperthyroidism. J Clin Endocrinol Metab. 2016;(4):1381–9. doi: http://dx.doi.org/10.1210/jc.2015-3644. PubMed.

11 Struja T, Kaeslin M, Boesiger F, Jutzi R, Imahorn N, Kutz A, et al. External validation of the GREAT score to predict relapse risk in Graves' disease: results from a multicenter, retrospective study with 741 patients. Eur J Endocrinol. 2017;(4):413–9. doi: http://dx.doi.org/10.1530/EJE-16-0986. PubMed.

12 Brix TH, Kyvik KO, Christensen K, Hegedüs L. Evidence for a major role of heredity in Graves' disease: a population-based study of two Danish twin cohorts. J Clin Endocrinol Metab. 2001;(2):930–4. doi: http://dx.doi.org/10.1210/jcem.86.2.7242. PubMed.

13 Brix TH, Hegedüs L. Twin studies as a model for exploring the aetiology of autoimmune thyroid disease. Clin Endocrinol (Oxf). 2012;(4):457–64. doi: http://dx.doi.org/10.1111/j.1365-2265.2011.04318.x. PubMed.

14 Hall R, Stanbury JB. Familial studies of autoimmune thyroiditis. Clin Exp Immunol. 1967;:719–25. PubMed.

15 Bona G, Defranco S, Chiocchetti A, Indelicato M, Biava A, Difranco D, et al. Defective function of Fas in T cells from paediatric patients with autoimmune thyroid diseases. Clin Exp Immunol. 2003;(3):430–7. doi: http://dx.doi.org/10.1046/j.1365-2249.2003.02221.x. PubMed.

16 Salmaso C, Bagnasco M, Pesce G, Montagna P, Brizzolara R, Altrinetti V, et al. Regulation of apoptosis in endocrine autoimmunity: insights from Hashimoto's thyroiditis and Graves' disease. Ann N Y Acad Sci. 2002;(1):496–501. doi: http://dx.doi.org/10.1111/j.1749-6632.2002.tb04253.x. PubMed.

17 Fountoulakis S, Vartholomatos G, Kolaitis N, Frillingos S, Philippou G, Tsatsoulis A. Differential expression of Fas system apoptotic molecules in peripheral lymphocytes from patients with Graves' disease and Hashimoto's thyroiditis. Eur J Endocrinol. 2008;(6):853–9. doi: http://dx.doi.org/10.1530/EJE-08-0092. PubMed.

18 Bacchetta R, Barzaghi F, Roncarolo MG. From IPEX syndrome to FOXP3 mutation: a lesson on immune dysregulation. Ann N Y Acad Sci. 2016 Feb 25 [epub ahead of print]. doi: http://dx.doi.org/10.1111/nyas.13011. PubMed.

19 Chistiakov DA, Chistiakova EI, Voronova NV, Turakulov RI, Savost'anov KV. A variant of the Il2ra/Cd25 gene predisposing to graves' disease is associated with increased levels of soluble inter-

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leukin-2 receptor. Scand J Immunol. 2011;(5):496–501. doi: http://dx.doi.org/10.1111/j.1365-3083.2011.02608.x. PubMed.

20 Wang Z, Fan X, Zhang R, Lin Z, Lu T, Bai X, et al. Integrative analysis of mRNA and miRNA array data reveals the suppression of retinoic acid pathway in regulatory T cells of Graves' disease. J Clin Endocrinol Metab. 2014;(12):E2620–7. doi: http://dx.doi.org/10.1210/jc.2014-1883. PubMed.

21 Singh K, Chang C, Gershwin ME. IgA deficiency and autoimmunity. Autoimmun Rev. 2014;(2):163–77. doi: http://dx.doi.org/10.1016/j.autrev.2013.10.005. PubMed.

22 Wang N, Shen N, Vyse TJ, Anand V, Gunnarson I, Sturfelt G, et al. Selective IgA deficiency in autoimmune diseases. Mol Med. 2011;(11-12):1383–96. doi: http://dx.doi.org/10.2119/molmed.2011.00195. PubMed.

23 Mohammadi J, Ramanujam R, Jarefors S, Rezaei N, Aghamohammadi A, Gregersen PK, et al. IgA deficiency and the MHC: assessment of relative risk and microheterogeneity within the HLA A1 B8, DR3 (8.1) haplotype. J Clin Immunol. 2010;(1):138–43. doi: http://dx.doi.org/10.1007/s10875-009-9336-2. PubMed.

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