



# Considerations for Use of Immune Checkpoint Inhibitors in Cancer Therapy for Patients with Co-Existing Thyroid Eye Disease

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## ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionised the field of oncology. While most ICIs are well-tolerated, severe and fatal immune-related adverse events (irAEs) have been documented, likely related to the strengthened immunity harnessed by ICIs against tumours. Endocrinopathies are some of the most common irAEs, with both hypothyroidism and hyperthyroidism encountered after ICI use. As such, patients with pre-existing autoimmune conditions, such as Graves' disease (GD) with clinically active thyroid eye disease (TED), are excluded from most clinical trials studying ICIs due to concerns of exacerbating pre-existing autoimmune conditions or of increasing the potential for irAE development. The limited information currently available on the safety and efficacy of ICIs in this population poses a clinical challenge for oncologists. The objective of this commentary is to highlight these challenges and provide treatment

recommendations pertaining to two specific cohorts of patients with GD, namely GD patients with minimal eye complications and GD patients with previous TED who underwent radiotherapy, surgery or pulse methylprednisolone and whose disease is now quiescent, and to patients with subclinical autoimmune thyroid disease.

**Keywords:** Cancer treatment; Graves' disease; Immune checkpoint inhibitors; Immune-related adverse events; Thyroid eye disease

### Key Summary Points

Immune checkpoint inhibitors (ICIs) harness the body's immune system against tumours. Immune-related adverse events (irAEs) are a side effect of this mechanism of action.

Endocrinopathies are some of the most common irAEs. The occurrence of irAEs are more common in patients with pre-existing autoimmune diseases (ADs) than in patients without.

Use of immunosuppressants 2–4 weeks prior to and throughout ICI treatment has been proven to be effective in preventing exacerbations of pre-existing ADs.

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A personalised approach in the use of ICIs is thus required and highlights the importance of inter-disciplinary collaboration between clinical oncology and ophthalmology.

## DIGITAL FEATURES

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## INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionised the field of oncology. By blocking cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) pathways, ICIs have benefited patients with metastatic cancers in terms of significantly longer progression-free and overall survival [1–3]. However, while ICIs are mostly well-tolerated, severe and fatal adverse events have been documented. These immune-related adverse events (irAEs) are likely related to the strengthened immunity harnessed by ICIs against tumours. Endocrinopathies are some of the most common irAEs, with both hypothyroidism and hyperthyroidism encountered after ICI use [4]. The clinical manifestations of thyroid-related irAEs closely resemble autoimmune diseases but without the chronicity [5]. As such, patients with pre-existing autoimmune conditions, such as Graves' disease (GD) with clinically active thyroid eye disease (TED), are excluded from most clinical trials studying ICIs due to concerns of exacerbating pre-existing autoimmune conditions or of increasing the potential of irAE development [6]. The limited information currently available on the safety and efficacy of ICIs in this population poses a clinical challenge for oncologists. The objective of this commentary is to highlight the challenges and provide recommendations pertaining to two specific cohorts of patients with GD,

namely GD patients with minimal eye complications and GD patients with previous TED who underwent radiotherapy, surgery or pulse methylprednisolone (PMP) whose disease is now quiescent.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## GRAVES' DISEASE AND THYROID EYE DISEASE

### Immunopathogenesis

Autoimmunity is characterised by a failure in either central or peripheral tolerance. Central tolerance refers to the elimination of T-cell receptors with high complementarity and affinity to self-peptides on major histocompatibility complexes (MHC) in the thymus [7]. T cells with weak affinity are positively selected and further develop into CD8 T cells or CD4 T cells depending on the receptors' specificity to MHC Class I or II molecules, respectively. In the case of fallible self–nonself discrimination in the thymus, various immune checkpoint pathways regulate T-cell activation. Crucial to this process of peripheral tolerance are the CTLA-4 and PD-1 immune checkpoint pathways. Both act as a negative costimulatory signal to inhibit T-cell activity at different phases of activation (priming vs. effector) and at different anatomical locations [7]. CTLA-4 on activated T cells and regulator T cells (Treg) mediate immunosuppression through direct and indirect down-regulation pathways. The direct interaction between CTLA-4 and B7 ligands on the surface of antigen-presenting cells induces T-cell anergy [8]. By binding with much higher affinity than and outcompeting the costimulatory receptor CD28, CTLA-4 indirectly increases the activation threshold of T cells and dampens immune responses against self-antigens [9, 10]. In comparison, PD-1, which is similar to CTLA-4 in structure and binding, antagonises TCR-CD28 signals via PD-1–PD-1L interactions [11], leading to a reduction in T-cell proliferation and survival, as well as cytokine production [7].

GD is characterised by the loss of tolerance to self-antigens in T cells, most commonly the thyroid-stimulating hormone receptor (TSHR). The activated helper T cells and their subsequent production of cytokines (interleukin [IL]-2, -4, -5) stimulate B cells to produce TSHR autoantibodies, which bind to and mimic the effect of thyroid hormone on the thyrotropin receptors. TED is an ocular inflammatory disease commonly associated with GD in which TSHR is also the primary autoantigen [12]. Clinically identifiable TED occurs in 40% of patients with GD, with common orbital and periorbital manifestations being eyelid retraction, proptosis, diplopia and increased intraocular pressure [13]. TED typically follows a biphasic course, with an initial active inflammatory phase and an ensuing static fibrotic phase [14]. The first phase reflects inflammatory changes induced by the activation of orbital fibroblasts by the TSHR autoantibodies. The release of proinflammatory mediators, compounded by the infiltration and interaction of immunocompetent T helper (Th1) and B lymphocytes, macrophages and mast cells, contribute to the enhanced adipogenesis that interferes with orbital functions [15].

### Conventional Treatments for Thyroid Eye Disease

Treatment of TED requires a multidisciplinary effort from ophthalmologists, endocrinologists and radiologists. The primary goal is to restore a euthyroid state and to prevent sight-threatening ocular complications.

Treatment modalities for TED depend on the severity and activity of the disease. For mild TED, local supportive measures are the mainstay treatment. In one randomised controlled trial (RCT), selenium supplementation was shown to improve ocular parameters and quality of life in patients with mild TED when compared with placebo [16]; however, the lack of data on serum selenium levels and the possibility of marginal selenium deficiency in the patients tested may have skewed the data. For patients with moderate and severe TED, current treatment strategies focus on

immunosuppression in the active phase. Systemic glucocorticoids are regarded as the first-line treatment, with weekly intravenous pulse treatment being favoured over oral treatment due to its higher efficacy and fewer adverse effects [17, 18]. The improvement in ophthalmic symptoms is thought to be due to inhibited transcription of intra- and extracellular proinflammatory proteins in orbital fibroblasts and Th1 lymphocytes [15]. If the patient is intolerant or the TED is refractory to steroids, second-line medical therapies include combination therapy with steroid-sparing agents, such as cyclosporine and azathioprine.

These well-established treatment modalities do not minimise the likelihood of patients requiring subsequent rehabilitative surgery for residual disfigurements and dysfunction. Therefore, there is a need for more targeted therapeutics. Biological agents, such as rituximab (humanised chimeric monoclonal anti-CD 20 antibody), despite a compelling mechanism of action, have demonstrated conflicting results in two RCTs [19, 20]. However, it is worth noting that the small sample sizes and the differences in baseline parameters of the patients recruited to these two RCTs may account for the discrepancy. Results from small case studies have also supported the use of immunomodulatory agents targeting key cytokines—IL-1, IL-6 and tumour necrosis factor-alpha. A new targeted therapy involving teprotumumab, a fully human IgG1 monoclonal antibody directed against the insulin-like growth factor 1 receptor, has demonstrated promising results in reversing diplopia and proptosis in two multinational RCTs [21, 22], but the clinical use of this monoclonal antibody, especially in public healthcare systems, is limited by its high costs. Orbital radiotherapy is also indicated if there is involvement of extraocular muscle, with a modest effect on motility and proptosis [23], but surveys of European and American specialists indicate that this therapy is generally considered as a second- or third-line treatment [24, 25]. Acute side effects of orbital radiotherapy, such as periorbital oedema and conjunctival injection, are common and self-limiting [23], but long-term side effects, such as cataract, retinopathy and

radiation-induced tumours post-radiotherapy, have been reported [23, 26].

For sight-threatening TED, including dysthyroid optic neuropathy, treatment is more aggressive, involving decompression through a combination of high-dose intravenous methylprednisolone and orbitotomy. Severe complications have been reported, which include acute liver damage, cardiac arrhythmias, hypertension, diabetes mellitus and osteoporosis following PMP and diplopia with orbital decompression [27–29].

## USE OF IMMUNE CHECKPOINT INHIBITORS AND THYROID EYE DISEASE-LIKE IMMUNE-RELATED ADVERSE EVENTS

Immune checkpoint inhibitors have emerged as a major pillar of modern cancer treatment. Neoplastic cells utilise physiological immune checkpoint pathways against autoimmunity to elude immunosurveillance. Through targeting the CTLA-4 and PD-1 immune checkpoint pathways, ICIs fundamentally upregulate the host's immune system and mediate an antitumour response. Briefly, CTLA-4 blockade causes effector T cells at the priming phase to activate and proliferate, and reduces Treg-mediated suppression of T-cell responses [7, 30]. PD-1 blockade affects T cells at the effector phase and reverses T-cell exhaustion [31]. Since PD-L1 is expressed on cancer cells within the tumour microenvironment, PD-1 blockade confers a more specific and effective antitumour effect with less severe side effects [30]. Unfortunately, however, ICIs may be a double-edged sword. Tilting the balance of immune surveillance may perturb immunologic homeostasis. This is well-reflected by the emergence of irAEs. IrAEs have been reported in up to 80% of patients receiving these treatments, with a higher incidence in those receiving CTLA-4 inhibitors compared with PD-1 blockade [32]. While the exact pathophysiology of irAEs remains unclear, it is likely due to heightened T-cell activity against shared antigens, as well as elevated levels of

inflammatory cytokines and pre-existing autoantibodies [33].

Ocular irAEs are rare but potentially deleterious. Dry eyes, uveitis and myasthenia gravis with ocular involvement are commonly reported ocular toxicities [34, 35]. TED-like orbital inflammatory syndrome has also been described in case studies [36–39]. Patients on anti-CTLA4 or anti-PD1 therapy with no history of thyroid disease have developed TED-related inflammatory symptoms with fusiform enlargement of rectus muscles involving muscle bodies and sparing the tendons. However, these patients had variable thyroid hormone profiles. Most were euthyroid with elevated thyroid antibodies (particularly anti-thyroid peroxidase and anti-thyroglobulin antibodies, occasionally anti-TSHR), and some patients had hyperthyroidism [36–39]. The majority of patients were managed successfully with systemic steroid treatment. Relapse and persistence of ocular symptoms after tapering of steroids has also been encountered [38]. The decision of whether/when to discontinue ICIs is not unanimous among clinicians, in part due to the concern that the systemic steroid may reverse the antitumour activity of ICIs.

The association between ICIs and TED may be related to allelic variants of the *CTLA-4* and *PD-1* genes. Genetic analyses over the last decade have established that *CTLA-4* gene polymorphisms confer susceptibility to GD. Well-studied polymorphisms include an adenine-to-guanine single-nucleotide polymorphism (SNP) at position 49 in the CTLA-4 leader peptide (A/G<sub>49</sub>), a 3' untranslated region (3' UTR) microsatellite [(AT)<sub>n</sub> repeat] of exon 4 and a cytosine-to-thymine substitution at position -318 of the promotor region (C/T<sub>-318</sub>) [40]. The functional significance of these polymorphisms has been investigated in various case control studies, mainly relating to the reduced expression levels and function of CTLA4 [41–43] and production of thyroid autoantibodies (TAb) [40, 44]. Regarding the association of these genetic modifications with TED, a meta-analysis with 14 case-control studies demonstrated an increased risk of TED with the CTLA-4 A/G<sub>49</sub> SNP in both Caucasian and Asian populations [45]. A case-control study on Taiwanese

patients in 2019 identified the CTLA-4 promoter -1722 polymorphism, notably the TT genotype, and its relationship to an increased risk of TED [46]; however, these authors found no correlation between TED and the A/G<sub>49</sub> SNP in exon 1.

The differences in genotypes and phenotypes may be accounted for by linkage disequilibrium, male-to-female ratio and the definition of TED [47]. Correlation studies on the polymorphisms and the molecular pathophysiology of TED have shown that the allelic variations in the promoter (-1722) and exon 1 (A/G<sub>49</sub>) reduce the transcription and expression of CTLA-4 [41, 48]. Since the exon 1 polymorphism (A/G<sub>49</sub>) also weakens the downstream signalling of CTLA-4, the aggregate effect reduces immune tolerance to self-antigens, namely TSHR. Correlations between TED and PD-1 genetic polymorphisms have also been identified in case-control studies. In a UK GD dataset of 2671 patients, two of the eight investigated tag SNPs were significantly associated with GD, but not with TED [49]. PD-1L A/C polymorphisms at position 8923 of intron 4 and their association with GD have also been demonstrated in Japanese and European patient cohorts [50, 51]. TED was used as one of the selection criteria for GD subjects in the European study, but the association between the polymorphism and TED was not explored [50].

The occurrence of irAEs are more common in patients with pre-existing autoimmune diseases (ADs) than in to patients without [6]. Yet, flares are mild to moderate in severity and are mostly controlled by standard treatment. ICI discontinuation is often not required, and efficacy of ICIs remain comparable between patients with and without pre-existing ADs. The pre-existing ADs that extant literature focus on are of a rheumatological (e.g. psoriasis, rheumatoid arthritis and systemic lupus erythematosus) and gastrointestinal nature (e.g. inflammatory bowel diseases) [6]; thyroid diseases are less common. This could reflect the prevalence of AD or the more severe or active presentation of these patients which deters oncologists from ICI use. Therefore, there remains a need to characterise patients with GD who may be eligible for ICIs. In this context, two specific cohorts of GD

patients have been identified: (1) GD patients with minimal eye complications, and (2) GD patients with previous TED who underwent radiotherapy, surgery or PMP and whose disease is now quiescent.

It is important to recognise a third cohort of patients, those with subclinical autoimmune thyroid disorders. There remains uncertainty over the clinical utility of managing thyroid dysfunction in this patient population on the basis of biochemical derangements [52]. However, given the possibility of progression to overt disease, clinicians should also investigate these patients for parenteral and family anamnesis of autoimmune diseases. The limited data available from clinical trials on the aforementioned two patient populations highlight the need for high-quality clinical trials to focus on these cohorts. However, extrapolating and utilising existing recommendations for ICI administration in active pre-existing AD indicates that a personalised and stepwise strategy is optimal.

**Personalised Strategy** It is important to recognise that the clinical manifestation of GD or TED is multifactorial and involves an intricate interaction between genetic, immunological and environmental factors, particularly smoking. Given the complexity of the tumour microenvironment and the dynamic interaction of inflammatory molecules in patients with autoimmune thyroid disorders, the choice of selective immunosuppressants may impact the efficacy of treatment. Anti-IL-6 receptor antibodies could preferentially be used in high-risk patients. IL-6, a paracrine and autocrine cytokine, has been speculated to be crucial in the pathophysiology of Graves' ophthalmopathy, with higher serum concentrations in patients with active ophthalmopathy [53, 54]. The blockade of IL-6 and the PD-1 axis has been shown to have synergistic antitumour effects through the induction of cytotoxic T cells and the inhibition of *in vivo* tumourigenesis in animal studies [55, 56]. Anti-IL-6 receptor antibodies have also yielded rapid and sustained improvement in various ocular parameters in patients with refractory Graves' orbitopathy [57]. A personalised strategy for patients highlights the importance of inter-disciplinary

collaboration between clinical oncology and ophthalmology. An effective multidisciplinary clinical pathway for these patients should be established.

**A Stepwise Approach** The chronology with which medications are given may render ICIs safe and effective. By replacing a non-specific immunosuppressant (e.g. steroids) with a selective immunosuppressant (e.g. infliximab, tocilizumab, vedolizumab) 2–4 weeks prior to and throughout ICI treatment, patients have shown optimal response with an absence of autoimmune disease exacerbations [6].

## CONCLUSIONS

In conclusion, endocrinopathies are some of the most common irAEs. It is also important to note that patients with pre-existing GD are more likely to suffer from acute exacerbation of illness. Thus, a personalised approach in the use of ICIs in the context of GD and other autoimmune diseases is required. This highlights the importance of inter-disciplinary collaboration between clinical oncology and ophthalmology.

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