treatment with a multidisciplinary team, which should include an endocrinologist.

During ICI treatment, it is generally advised to monitor TSH and fT4 prior to every ICI treatment cycle during the first 6 months, after which the interval can be prolonged to every 2–3 months for 6 months and every 6 months thereafter. In case of discrepant test results or non-concordance between clinical and biochemical findings, assay interference should be suspected (80). In case of thyrotoxicosis, guidelines generally recommend TSH receptor-antibody testing. In case of hypothyroidism, TPO-antibody testing is recommended as it indicates autoimmune etiology. Most guidelines do not recommend thyroglobulin antibody testing. Since cases of Graves' disease have been described without increased levels of TSH receptor antibodies (58), fT3 testing, thyroid scintigraphy, and ultrasonography are useful for differentiation in cases of severe or prolonged thyrotoxicosis.

Treatment considerations

Most cases of thyrotoxicosis can be treated with beta-blockers for symptomatic relief. Graves' disease requires treatment with anti-thyroid drugs. Primary hypothyroidism is treated with levothyroxine aiming at normalisation of TSH values.

Summary of evidence

Eight studies reporting on levothyroxine replacement therapy could be included in our systematic review (57, 62, 65, 68, 69, 81, 82, 83). In a substantial number of patients, thyroid dysfunction was reported, ranging from 14 to 33%. See Supplementary Tables 3 and 4 for details. A presentation with thyrotoxicosis first or hypothyroidism was both often reported. In some studies, all patients required levothyroxine replacement, while in other studies the percentages varied between 20 and 84%, especially in patients with mild subclinical hypothyroidism. Recovery after thyrotoxicosis was reported in up to 57%; some patients that did recover received high-dose glucocorticoids for other immune-related adverse events (57). However, most patients with hyperthyroidism progressed to hypothyroidism. Recovery from hypothyroidism was only rarely reported.

A retrospective analysis of high-dose glucocorticoid treatment of ICI-related thyroid disorders (15 patients treated vs 38 patients not treated with high-dose glucocorticoids) concluded that glucocorticoids did not prevent or reduce ICI-induced thyroid damage. There was no difference in maintenance dose of levothyroxine between patients receiving high-dose glucocorticoids (1.5 µg/kg/d, range 0.4–2.3) and those who did not (1.3 µg/kg/d, range 0.3–2.5), nor in time to onset of thyrotoxicosis, time to conversion to hypothyroidism, or time to onset of hypothyroidism (79). However, most studies did not apply high-dose glucocorticoid therapy. Prospective randomized studies are needed in order to evaluate whether high-dose glucocorticoids should be used in selected subgroups of patients with ICI-induced thyroid dysfunction to improve the outcome.

Recommendations for treatment and follow-up

R 3.1 - We recommend against the use of high-dose glucocorticoids for the treatment of thyroiditis; except in severe thyrotoxicosis and severe thyroid eye disease (+000).

Rationale: There is no evidence for treatment efficacy of high-dose glucocorticoid therapy. Moreover, such treatment can induce secondary adrenal insufficiency if doses of prednisolone > 7.5 mg per day are given for longer than 2–3 weeks. In cases of severe thyrotoxicosis, high-dose glucocorticoids reduce T4 to T3 conversion. Cases of ICI-related thyroid eye disease are extremely rare but can occur even in the absence of increased TSH receptor-antibodies and should be referred to an endocrinologist and ophthalmologist for shared decision regarding treatment with high-dose glucocorticoids.

R 3.2 - We suggest that cases of clinically and biochemically mild thyrotoxicosis or hypothyroidism can be monitored without treatment (good clinical practice).

Rationale: Most cases of thyroid dysfunction are mild. Monitor TSH and fT4 every 3–6 weeks in the early phase; the frequency can be lowered at later stages (depending on biochemical levels and trends) (84).

R 3.3 - We recommend using beta-blockers in symptomatic thyrotoxicosis (good clinical practice).

Rationale: Short-term treatment with a non-selective beta-blocker (e.g. propranolol) can be initiated to resolve symptoms of thyrotoxicosis. As most cases are caused by thyroiditis, anti-thyroid drugs are not indicated, except in rare cases of Graves' hyperthyroidism, which should be referred to an endocrinologist for shared care. Radioactive iodine and thyroid surgery are not recommended as first-line treatment of ICI-related thyrotoxicosis.

R 3.4 - We suggest replacement with levothyroxine in primary hypothyroidism in cases with fT4 below the lower reference limit and TSH > 10 mIU/L. (++00)

Rationale: Symptoms and signs of hypothyroidism are difficult to evaluate in an oncological setting, but