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NHS Foundation Trust

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Our Ref: [redacted]
Hospital No:
NHS No:
Date of clinic:
Date:

Private & Confidential

Dear Dr

Re: XXXXXXXX **DOB:**

Trust No NHS No Telephone No:

Thank you for your enquiry or referral to our department regarding the use of T3 (Liothyronine) as a therapy for primary hypothyroidism.

Summary of Advice

As a team, we do recognise that a small proportion of patients with primary hypothyroidism struggle with symptoms despite adequate biochemical replacement – however, any therapy for primary hypothyroidism other than T4 (Levothyroxine) lacks an evidence base and carries real clinical risks. Consequently, the position of the UHBW endocrine department is that, based on careful consideration of the currently available scientific evidence, we do not support the use of any T3 preparation in the treatment of thyroid disease, either alone or in combination with T4 as the clinical evidence shows the use of T3 to be no more effective than T4 alone.

For patients with persistent symptoms following biochemical optimisation of their T4 replacement therapy, we recommend that they should be thoroughly evaluated for any other potentially modifiable conditions. Particular attention should be paid to excluding those medical conditions that may occur more commonly in patients with hypothyroidism; for example, coeliac disease or anaemia secondary to B12 deficiency.

T3 therapy is more expensive than T4 but we would like to highlight that our decision has been made primarily based on the lack of supporting scientific evidence. We will proactively review our position as any new data become available. Our approach is in accordance with the available research evidence and is consistent with best practice guidelines.

Please do not refer patients to UHBW for consideration of T3 therapy – the only way for patients to access T3 would be to source it privately. We are more than happy for you to share this letter with your patient. A more detailed explanation with the relevant scientific references is outlined below.

Background

T4 is produced exclusively by the thyroid gland; its daily production rate being about 100 mcg in an average adult. The daily production rate of T3 is approximately 30 mcg; 20% is secreted by the thyroid gland, and 80% is generated in extra-thyroidal tissues by 5'-deiodination of T4. T3 is the active hormone but every target organ in the body that requires thyroid hormones can convert T4 to make T3.

The goal of therapy in hypothyroidism is restoration of the euthyroid state, which can be readily accomplished in almost all patients by oral administration of synthetic T4. Patients who are treated with T4 usually begin to improve within two weeks, but complete recovery can take several months in those with severe hypothyroidism. Steady-state TSH concentrations are not achieved for at least six weeks.

The average replacement dose of T4 in adults is approximately 1.6 mcg/Kg body weight per day, but older patients should be started on a lower dose (25 to 50 mcg daily) and gradually titrated up. This is especially important in patients with known or possible ischaemic heart disease. T4 should be taken on an empty stomach, ideally an hour before breakfast. T4 should not be taken with other medications or foodstuffs that interfere with its absorption, such as proton pump inhibitors, calcium or iron supplements, soya milk or caffeine. Appropriate treatment should reverse all the clinical manifestations of hypothyroidism. Approximately 80 percent of a dose of T4 is absorbed and because the plasma half-life of T4 is long (seven days), when a steady state is reached, a once-daily T4 tablet results in nearly constant serum T4 and T3 concentrations. For most patients on L-T4, brand or named supplier prescribing of T4 is not considered necessary. Rarely, patients may require a specific brand of L-T4 to be prescribed due to intolerance of generic preparations (Okosieme et al, Clinical Endocrinology: 2015).

As many symptoms of hypothyroidism are nonspecific, patients may feel that their T4 dose is inadequate in the context of concerns such as fatigue or unexplained weight gain. If a patient on treatment for hypothyroidism does have possible symptoms of under-activity and the serum TSH is confirmed to be towards the upper limit or above the normal reference range, it may be reasonable to increase the T4 dose and to aim for a serum TSH value in the lower half of the normal range. Once the TSH is within normal reference range, periodic (yearly, unless pregnancy is planned) monitoring is warranted.

It is also known that a small proportion of hypothyroid patients remain symptomatic despite achieving normal TSH concentrations on T4 replacement. This observation raises the question of whether hypothyroid patients might benefit from the addition of T3, an idea that has now been evaluated in multiple randomised trials, almost all of which showed that combination T4-T3 therapy does not appear to be superior to T4 monotherapy for the management of hypothyroid symptoms (Okosieme et al, Clinical Endocrinology: 2015). The half-life of T3 is short (about 1 day), and treatment with T3 requires several doses per day and still results in a wide variation in serum T3 levels during the 24-hour period. Of note, elevated serum T3 concentrations may occur during the absorption of T3, which can be associated with symptoms of hyperthyroidism and risks side-effects from slight over-treatment in the long term. These side-effects include atrial fibrillation (an erratic heartbeat which increases the risk of stroke) and loss of bone strength (increasing the

risk of osteoporosis and fractures). T4/T3 combination therapy is clearly advised against in pregnancy as T3 does not cross the placenta, so it will not support appropriate fetal neurodevelopment.

In a systematic review of nine randomised trials, only one of the nine reported beneficial effects of combination T4-T3 therapy on mood, quality of life, and psychometric performance when compared with T4 therapy alone (Escobar-Morreale et al, Journal of Clinical Endocrinology & Metabolism: 2005). A subsequent meta-analysis of 11 published randomised trials including 1216 patients showed that there was no benefit in terms of fatigue, bodily pain, anxiety, depression or overall quality of life from combined therapy (Grozinsky-Glasberg et al, Journal of Clinical Endocrinology & Metabolism: 2006).

Whether a combination of T4 and T3 is beneficial in a particular subset of hypothyroid patients remains uncertain. For example, the rs225014 polymorphisms in the type 2 deiodinase enzyme which converts T4 to T3 are estimated to occur in up to 16% of the population, and have been reported to be associated with an improvement in psychological well-being on combined T4-T3 therapy compared to T4 replacement alone therapy (Panicker et al, Journal of Clinical Endocrinology & Metabolism: 2009).However, this polymorphism had no impact on circulating thyroid hormone levels, hence routine clinical tests including measurement of T4 and T3 offer no guidance and so treatment of population sub-groups remains only a theoretical possibility currently (Carle et al, European Thyroid Journal: 2017).

The research data above refers to the use of synthetic human T3. It is worth highlighting that there are various desiccated non-human T3 preparations sold unlicensed in the UK (e.g. porcine Armour Thyroid) which contain excessive amounts of T3 in relation to the normal physiological human T4:T3 ratio.

Assuming serum TSH concentrations have been optimised to within the lower half of the reference range on T4, then other causes for any persistent symptoms should be considered and excluded. A general work-up should be undertaken to exclude well-known causes of non-specific symptoms that have nothing to do with thyroid disease such as anaemia, hypercalcemia, occult infections, adrenal insufficiency etc., as well as considering the possibility of any other associated autoimmune diseases since primary hypothyroidism is most commonly of autoimmune aetiology.

We hope that the above is helpful and highlight that our approach is consistent with the British Thyroid Association Position Statement (Okosieme et al, Clinical Endocrinology: 2015) which is endorsed by the Royal College of Physicians, the Society for Endocrinology, the British Thyroid Association, the British Thyroid Foundation Patient Support Group, and the Royal College of General Practitioners.

Yours sincerely

The UHBW Endocrine Team

cc: Notes