HHS Public Access

Author manuscript

Nephrol Dial Transplant. Author manuscript; available in PMC 2015 October 09.

Published in final edited form as:

Nephrol Dial Transplant. 2008 May ; 23(5): 1766–1768. doi:10.1093/ndt/gfm887.

Vasculitis and anti-thyroid medication

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Sir,

We appreciate the opportunity to respond to the comments made by Woywodt *et al*., regarding our evaluation of the association of thyroid disease and vasculitis [1]. Their major concern is that our study does not support our statement that the use of anti-thyroid agents does not account for many cases of ANCA-Small Vessel Vasculitis (ANCA-SVV) in the general population, a contention we continue to support.

Undoubtedly the relationship between thionimides, particularly propylthiouracil (PTU), and ANCA-SVV is well recognized with numerous cases reported in the literature, as well as a description and review of drug-induced vasculitis by our own group [2]. However, an abundance of publications does not translate to a high attributable risk of the disease from any specific cause. Continuous efforts to explore the aetiopathogenesis of ANCA-SVV require studies of well-defined cohorts of patients with histological proof of disease, with comparisons to population-based controls required to quantify the absolute risk ascribed to specific exposures. Furthermore, definitive proof would necessitate identification of derived PTU-reactive intermediates, specifically at the sites of disease. The examples provided by Woywodt *et al*. in support of the association between anti-thyroid treatment and ANCA and/or vasculitis are among cohorts limited to patients with thyroid disease. Although these cohorts provide insights into the mechanisms and prevalence within thyroid disease patients, by design they do not portend an understanding of risk in the general population or even among patients with ANCA-SVV. Likewise, the example of the high odds ratio of 11.8 (95% CI 1.5 to 93.3, P=0.005) emphasizes the strong association, albeit lack of precision between anti-thyroid treatment and ANCA positivity (not ANCA-SVV) among patients with hyperthyroidism [3]. What is masked by the high odds ratio is the low frequency of ANCA positivity, with only 13 of 206 patients (6.3%) becoming ANCA-positive; 11 of 107 (11%) previously treated with thionomides and 2 of 100 (2%) with no anti-thyroid drug exposure.

Conflict of interest statement. None declared.

Notably the proportion of patients who become ANCA-positive after therapy with thionomides varies substantially across studies [3–5]. A prospective study of 102 patients, all of whom were ANCA-negative at presentation, revealed that only 3 (3%) patients became ANCA-positive following treatment with PTU, with 2 becoming ANCA-negative over time despite continuation of the drug [4]. But even when the reported incidence of ANCA positivity among patients treated with thionimides is considerably higher, the number of patients who develop ANCA-SVV is remarkably small [3,5]. Sato *et al*. report that 16 of 25 (64%) hyperthyroid patients became ANCA-positive after therapy with thionimides, but none developed ANCA-SVV [5]. In the study by Slot *et al.*, 11 of 107 (11%) thionamide-treated patients became ANCA-positive, with only 3 (3%) having biopsy-proven ANCA-SVV [3]. Interestingly, ANCA positivity has also been reported in patients with Grave's disease who have not been treated with thionimides [3,5]. Whether other factors such as genetic influences and the nature and/or activity of the thyroid disease itself play a role in the development of ANCA-SVV remains to be investigated.

Beyond this, we cannot ignore the established phenomenon of overlapping syndromes of systemic and organ-specific autoimmune diseases. Among others, Biro *et al.*, in a population of 1517 patients with various autoimmune diseases, found that the prevalence of Hashimoto's thyroiditis or Grave's disease was 8.2% [6]. In the same study, among 426 patients followed in their thyroid clinic, a 30% incidence of systemic autoimmune disease was observed [6].

Woywodt *et al*. also question our method of collecting medical and treatment history via telephone interviews. We concur that recall bias is a concern in any case-control study and can lead to spurious associations. The best defense against recall bias is the confirmation of information through a separate source. In our study, we were able to review medical records among 52% of case participants, with the history of thyroid disease (or not) and use of specific reported drugs confirmed in 100% of available records. With respect to controls, medical records were not available, but our estimates were similar to well-defined population estimates [7]. These statistics give us reasonable confidence that recall was not a major issue in our study.

In summary, the literature suggests that there is a strong association between anti-thyroid drugs and vasculitis, but we maintain that our population-based study suggests that only a small portion of ANCA-SVV can be associated with this drug. We also stand by our recommendation for monitoring the development of ANCA and early symptoms of systemic vasculitis among individuals with thyroid disease, not just those treated with thionimides. However, other 'triggers' for the onset of ANCA-SVV, such as a concurrence of two or more autoimmune diseases, with our example of a history of thyroid disease found in as many as 40% of ANCA-SVV female patients [1], and high silica exposure found in up to 47% of ANCA-SVV patients [8], are far more likely to contribute to the development of ANCA-SVV in the general population.

References

1. Lionaki S, Hogan SL, Falk RJ, et al. Association of thyroid disease and its treatment with the onset of ANCA small-vessel vasculitis. Nephrol Dial Transplant. 2007; 22:3508–3515. [PubMed: 17686815]
2. ten Holder SM, Joy MS, Falk RJ. Cutaneous and systemic manifestations of drug-induced vasculitis. Ann Pharmacother. 2002; 36:130–147. [PubMed: 11816242]
3. Slot MC, Links TP, Stegeman CA, et al. Occurrence of antineutriphil cytoplasmic antibodies and associated vasculitis in patients with hyperthyroidism treated with antithyroid drugs: a long-term followup study. Arth Rheum. 2005; 53:108–113. [PubMed: 15696557]
4. Noh JY, Asari T, Hamada N, et al. Frequency of appearance of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) in Graves' disease patients treated with propylthiouracil and the relationship between MPO-ANCA and clinical manifestations. Clin Endocrinol (Oxf). 2001; 54:651–654. [PubMed: 11380496]
5. Sato H, Hattori M, Fujieda M, et al. High prevalence of antineutrophil cytoplasmic antibody positivity in childhood onset Graves' disease treated with propylthiouracil. J Clin Endocrinol Metab. 2000; 85:4270–4273. [PubMed: 11095466]
6. Birö E, Szekanecz Z, Czirják L, et al. Association of systemic and thyroid autoimmune diseases. Clin Rheumatol. 2006; 25:240–245. [PubMed: 16247581]
7. Cooper DS, Ridgway EC. Thoughts on prevention of thyroid disease in the United States. Thyroid. 2002; 12:925–929. [PubMed: 12487775]
8. Hogan SL, Cooper GS, Savitz DA, et al. Association of silica exposure with ANCA small vessel vasculitis: a population-based case-control study. Clin J Am Soc Nephrol. 2007; 2:290–299.10.1093/ndt/gfm887 [PubMed: 17699427]