

DEVELOPMENT OF AUTOIMMUNE THYROID DISEASES DURING LONG-TERM TREATMENT OF HEMATOLOGICAL MALIGNANCIES WITH α -INTERFERONS

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ABSTRACT

In recent years recombinant α -interferons (α -IFNs) have been widely used in the treatment of several hematological malignancies. Prolonged courses of IFN have been shown to induce autoantibodies and to support the exacerbation or even the development of autoimmune diseases. In this report we describe the development of symptomatic autoimmune thyroid diseases in 4 (7.4%) out of 54 patients in chronic treatment with recombinant α -IFNs in our department.

Two patients developed a disease resembling Hashimoto's thyroiditis after 17 and 49 months of continuous IFN treatment, while the other two developed a typical Graves' disease after 41 and 52 months of therapy. The mechanism by which IFN induces autoimmune thyroid diseases, the choice of searching for anti-thyroid autoantibodies before starting long-term IFN treatment, the option of discontinuing IFN therapy in the presence of overt thyroid diseases, and the management of these diseases are discussed.

Key words: autoimmune thyroid diseases, α -interferon therapy

In recent years, recombinant α -interferons (α -IFNs) have been widely used in the treatment of an increasing number of hematological malignancies, such as chronic myeloid leukemia (CML),¹⁰ essential thrombocythemia (ET),¹¹ hairy cell leukemia (HCL),⁹ multiple myeloma (MM)¹⁴ and chronic lymphocytic leukemia (CLL).⁵

While the acute side effects of IFNs are well known, there have been few reports on adverse side effects during long-term treatment. However, prolonged courses of IFN have been shown to induce autoantibodies such as antinuclear, anticytoplasmic and antithyroid antibodies,^{3,16} and several investigators have reported the exacerbation or even the development of autoimmune diseases during IFN therapy.^{1,2,4,17,21,23,24}

In this report we briefly describe the development of symptomatic autoimmune thyroid diseases in 4 patients in chronic treatment with recombinant α -IFNs.

Case reports

Patient #1. MF, a 52-year-old woman, had a history of previous thyropathy (hyperthyroidism) between the ages of 20 and 35 years. She was diagnosed as suffering from Philadelphia positive (Ph1⁺) CML in August 1990. After a period of cytoreductive chemotherapy with hydroxyurea, she was started on α 2a-IFN (Roferon-A, Roche, Milano, Italy) therapy in November 1990, and rapidly reached the maintenance dose of 9 MU daily. In four months she experienced a complete hematological response. She was well till April 1992, when she began complaining of increasing fatigue, cold intolerance

ance, lethargy and weight increase.

Laboratory tests performed at that time showed: TSH > 40 mU/L (normal value <4.5), T3 0.34 ng/mL (0.6-1.8), and T4 8 ng/mL (45-120). Anti-thyroid microsomal antibodies were positive at 1/6400 and anti-thyroglobulin antibodies 1/20. Antinuclear, antiplatelet, and antiparietal cell autoantibodies were also positive. A diagnosis of primary hypothyroidism due to Hashimoto's thyroiditis was made and the patient was put on replacement therapy with L-thyroxine, 100 μ g daily. T3, T4 and TSH were normal by August 1992 and the patient was asymptomatic. Due to her underlying hematological disease, α 2a-IFN therapy was continued. In March 1993, because of the absence of a karyotypic response (100% Ph1⁺ metaphases), she was put on lymphoblastoid-IFN (Wellferon, Wellcome, Pomezia-Roma, Italy). At present, after 18 months of replacement therapy, she is still asymptomatic, euthyroid and on maintenance therapy with L-thyroxine, 75 μ g daily.

Patient #2. MM, a 56-year-old woman, was diagnosed as suffering from Ph1 negative CML in August 1987. She was started on α 2a-IFN therapy and rapidly reached the maintenance dose of 9 MU daily. Within four months she achieved a complete hematological response. In August 1989, due to the worsening of an apparently idiopathic atrial and ventricular tachyarrhythmia present since 1975, she was seen by a cardiologist and put on amiodarone therapy.

In January 1991 she began complaining of fatigue. T3 and T4 levels were within the normal range but TSH was 48 mU/L. This picture of *minimal hypothyroidism* was thought to be caused by the amiodarone, which was then stopped. In September 1991 she complained of increasing fatigue with proximal muscle weakness, cold intolerance, hair falling out, lethargy and weight increase. TSH was above the normal range (24.5 mU/L), T3 was 1.4 ng/mL and T4 43 ng/mL. Autoantibodies were as follows: antimicrosomal 1/6400; antithyroglobulin 1/1280; antinuclear and antiparietal cell positive. A diagnosis of primary hypothyroidism due to Hashimoto's thyroiditis was made; α -IFN was stopped and, since January 1992, the

patient has been on replacement therapy with L-thyroxine, 100 μ g daily. Two months later she was asymptomatic and thyroid hormone levels were within the normal range. At present, after 22 months of replacement therapy, she is still euthyroid, in therapy with L-thyroxine 75 μ g daily, and in hematological remission.

Patient #3. SV, a 56-year-old man, was diagnosed as suffering from HCL in September 1988. In November 1988 he was started on α 2b-IFN (Intron-A, Schering-Plough, Milano, Italy) 3 MU daily, then reduced to a maintenance dose of 1.5 MU three times a week in July 1989. He never reached complete hematological remission and presented a chronic mild leukopenia, but he was asymptomatic. In April 1993 he began complaining of increasing fatigue, weight loss, nervousness, emotional lability and palpitations. Physical examination revealed exophthalmos, tachycardia and thyroid enlargement. Thyroid laboratory tests showed a picture of thyroid hyperfunction: TSH < 0.1 mU/L, T3 4.2 ng/mL, T4 196 ng/mL. Anti TSH-receptor autoantibodies were present at high titre: 62.6 U/L (n.v. < 15 U/L). A diagnosis of Graves' disease was made; IFN was stopped and the patient was put on treatment with propylthiouracil (PTU) 100 mg daily (due to the presence of mild leukopenia, PTU was preferred to the standard treatment with methimazole, which is well known as a drug that depresses granulopoiesis) and propranolol. The patient returned to being euthyroid within two months. Two months after stopping IFN he was started on pentostatin (4 mg/m² every two weeks for 6 courses) to treat his HCL. After completing this regimen he achieved a complete hematological remission. At present, after six months of thyreostatic treatment, he is asymptomatic, euthyroid and still on maintenance therapy with PTU 50 mg daily.

Patient #4. UR, a 59-year-old man, was diagnosed as suffering from stage 0 CLL in April 1989. He was started on α 2b-IFN, 3 MU daily, which he continued for 1 year. In May 1990, because of a major hematological response (i.e. normalization of his full blood count, with only mild relative lymphocytosis), he was put on a maintenance program of 3 MU three times a week.

In December 1992, while in hematological remission, he began complaining of fatigue, weight loss, an inability to sleep, emotional lability and dyspnea. In January 1993, he presented acute atrial fibrillation. Physical examination showed mild exophthalmos, atrial fibrillation and very mild thyroid enlargement. Thyroid laboratory tests performed at that time showed a picture of thyroid hyperfunction: TSH < 0.1 mU/L, T3 31 ng/mL and T4 155 ng/mL. Anti-TSH-receptor autoantibodies were present at high titre: 43.9 U/L. A diagnosis of Graves' disease was made; IFN treatment was stopped and the patient was put on methimazole, 20 mg daily for 20 days, then 5 mg daily as maintenance. He was anticoagulated with dicumarol and underwent electrical cardioversion.

At present, after 10 months of thyreostatic treatment, he is asymptomatic, euthyroid, still on maintenance therapy with methimazole and in stage 0 CLL.

Discussion

The mechanism by which IFN induces autoimmune thyroid diseases is unclear. A crucial step seems to be the induction of HLA class I expression on the surface of thyroid cells. The expression of MHC molecules on cell surfaces, in association with normal cellular antigens, might be sufficient to break tolerance and induce autoantibody formation and activation of cytotoxic or suppressor T lymphocytes and NK cells. Hyperthyroidism and goiter in Graves' disease are caused by thyroid-stimulating autoantibodies that bind to and activate the thyroid-stimulating hormone (TSH) receptors on thyroid follicular cells. Hypothyroidism in chronic autoimmune thyroiditis is caused by autoantibodies that block the binding of TSH to its receptors and by thyroid-cell death due to an accumulation of lymphocytes, predominantly T cells, in the thyroid.²²

There have been several reports of thyroid diseases associated with interferons^{3,6-8,12,13,15,19,20} and other cytokine therapy.^{19,20} Most of these studies involved patients in chronic treatment with α -IFNs for chronic hepatitis or cancer. The incidence of thyroid diseases varied from 2.5% to 45%,^{3,6,12,18} and the time between start of therapy

and development of thyroid disease varied considerably, with intervals ranging from 6 weeks to 24 months.^{8,12}

In our Department 54 patients are currently in chronic treatment with α -IFNs for hematological malignancies such as CML, ET, HCL, MM and CLL. In this report we describe 4 of these patients (7.4% of the total), who developed a symptomatic autoimmune thyroid disease after 17, 49, 52 and 41 months of IFN treatment, respectively.

Two patients (#1 and #2) developed hypothyroidism and a syndrome resembling Hashimoto's thyroiditis; the other two (#3 and #4) developed a clinically apparent hyperthyroidism with the typical biochemical and serological features of Graves' disease. Thyroid biopsies were not performed to verify the diagnosis because the patterns of thyroid autoantibodies were characteristic. α -IFN treatment was discontinued in 3 of the patients, while in patient #1, affected by Ph1⁺ CML, it was continued in the hopes of attaining a karyotypic response. This decision was based upon the recent findings of the Italian Cooperative Study Group on CML, which show a great advantage in overall survival for patients who reach some karyotypic response under α -IFN treatment as opposed to those with no karyotypic conversion and treated with conventional chemotherapy.¹⁰ In all four of these patients the thyroid disease remained active even after IFN was stopped, but was eventually brought under control by treatment for the thyroid condition. All four are at present asymptomatic and euthyroid. Two (#2 and #4) are still in hematological remission after discontinuing IFN, and they do not require further therapy, while patient #3, affected by HCL, still needs treatment.

These observations raise several questions as to whether thyroid circulating hormone levels and autoimmunity screening tests should be performed before starting long-term treatment with α -IFNs, and questions regarding the management of overt thyroid diseases during the treatment itself.

The exacerbation of autoimmune diseases during IFN therapy,⁴ and in particular the onset of thyroid dysfunction in patients with previ-

ously subclinical autoimmune thyroid disease,¹⁹ or with a previous history of thyroid disease have already been reported. These data suggest that at least the presence of anti-thyroid autoantibodies must be carefully documented in patients undergoing α -IFN therapy, and that, possibly, something other than IFN should be employed if proof of thyroid autoimmunity is found. On the other hand, knowledge of the underlying hematological disease and the availability of different drugs active against it play a central role in the therapeutic strategy. For example, our patient #1 (Ph1⁺ CML and previous history of thyropathy) would have been treated with IFN anyway, due to the great advantage in overall survival that IFN offers over conventional chemotherapy for that disease.¹⁰ Vice versa, a patient with HCL and signs of autoimmune thyropathy should be treated with drugs other than IFN that are equally or even more active against that disease, such as pentostatin or 2CdA.

Regarding the management of overt thyroid diseases during long-term α -IFN treatment, a distinction must be made between glandular hyper- or hypofunction. In fact, while thyrotoxicosis is a potentially life-threatening condition that always requires discontinuation of IFN, a different approach could be used in the case of hypothyroidism. Due to the availability of efficient replacement therapy, the decision about whether to discontinue IFN should be based upon knowledge of the underlying disease and the availability of active drugs other than IFN. Once again, our patients #1 and 2 fit this example, since IFN treatment was continued in the patient with Ph1⁺ CML and discontinued in the latter, where it was not strictly required.

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