Autoimmune Thyroid Disease in Patients with Philadelphia-Negative Chronic Myeloproliferative Neoplasms Treated with Interferon-Alpha

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Abstract

Objectives: Interferon-alpha (IFN-α) is increasingly being used in the treatment of the Philadelphia-negative chronic myeloproliferative neoplasms (MPNs). However, some 20% of patients discontinue treatment because of side effects, including thyroid dysfunction.

Methods: This retrospective study reports patients with MPNs who developed autoimmune thyroid disease (AITD) during treatment with IFN-α, representing 5.0% of the cohort (n=160).

Results: Eight patients (seven women) developed AITD with positive thyroid peroxidase antibodies. Seven patients had polycythemia vera (PV) and one essential trombocythemia (ET). The patients were younger than average and developed AITD 5-86 months after initiation of IFN-α, six within 15 months. In two patients, thyroid-stimulating hormone normalized after decreasing dosage of IFN-α and discontinuation of treatment, respectively.

Conclusion: This report underscores the importance of monitoring thyroid function before and during therapy, since the side effects of IFN-α may mimic thyroid disease. Although discontinuation of IFN-α therapy should be considered, it is possible to continue treatment.

Keywords

Philadelphia-negative chronic myeloproliferative neoplasms; Essential trombocythemia; Polycythemia vera; Myelofibrosis; Interferon alpha; Autoimmune thyroid disease; Hypothyroidism; Hyperthyroidism

Introduction

The Philadelphia-negative chronic myeloproliferative neoplasms (MPNs) include essential trombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) [1,2], and arise due to an acquired stem cell lesion with acquisition of various mutations, in particular JAK2V617 and CALR [3]. The morbidity is dominated by thrombosis and hemorrhage. Cytoreduction and aspirin decrease the risk of vascular events, and cytoreduction reduces hypermetabolic symptoms as well [1,4].

Interferon alpha (IFN-α) is being used increasingly in the treatment of patients with MPNs, in particular in younger patients. The rationales for its use are several, including its potent antiproliferative, proapoptotic, antiangiogenic and not least immunomodulatory properties [5,6]. Thus, IFN-α is considered to enhance the immune response against mutated cells as evidenced by a substantial reduction in the JAK2V617F allele burden in the large majority of patients [5,7], which is a major breakthrough in the treatment of MPNs [5,6,8].

Approximately 20% of patients are urged to discontinue treatment with IFN-α because of side effects [5]. More than 50 different side effects have been recorded, the most well-known being fatigue and flu-like symptoms, whereas there has been less focus on thyroid disease [9]. One study of a large cohort of MPNs reported thyroid disease in 10% during non-pegylated IFN-α therapy [10]. Fatigue in the MPN-patient may be integrated in the complex symptom burden, may be a side effect to the treatment with IFN-α due to a systemic inflammatory response or may actually reflect thyroid dysfunction elicited by IFN-α. Accordingly, it is of utmost importance to focus on the possibility of thyroid dysfunction in IFN-α-treated patients, because treatment is simple and can improve the patient’s quality of life. The most frequent indication for IFN-α is hepatitis C infection [11], where thyroid complications are well known and genetically predisposed patients may develop autoimmune thyroid disease [12-14]. The purpose of this retrospective study is to describe in further details patients with MPNs who develop autoimmune thyroid disease (AITD) during treatment with IFN-α.

Materials and Methods

This is a retrospective review of hospital journals and was conducted from March 1st to May 1st 2013, with a two year period of follow-up of index patients. Included patients in this cross-sectional cohort analysis (a) had been diagnosed with MPN in accordance with current diagnostic MPN criteria, (b) had been treated with IFN-α 2a or 2b and (c) had developed thyroid abnormalities identified with blood samples after initiation of IFN-α treatment. Twenty patients were identified in this cohort who had MPN and thyroid disease, but not all were treated with IFN-α or had thyroid disease prior to the treatment (n=12). Eight patients met all the criteria and were included. The patients were included from Department of Hematology, Rigshospitalet, Copenhagen (n=5) and from the Department of Hematology, Roskilde Hospital, Denmark (n=3). A total of 160 patients, 76 M and 84 F, mean age 56 years, range 21-86 years-old, were treated with IFN-α at Roskilde and Rigshospitalet. Some 70% of the patient population treated with IFN-α had PV. Laboratory analyses were performed by standard methods.

Results

The patients had been diagnosed with PV from 1996 to 2011, and all fulfilled WHO criteria [2]. The six females and one male had a median age at diagnosis of PV of 43 years, the ET patient being 49 years old (Table 1). Female sex was more frequent in the index patients (78%) than in the cohort (84 F/160). Three patients were treated with IFN-α2a (Pegasys®), two patients with –α2b (Pegintron/Introna®) and three patients with both drugs in two different periods (Table 1).
levels from 4.5 to 100 mU/l (Table 1). All patients had elevated levels. The 7 patients developing hypothyroidism had elevated TSH virtually unchanged cell counts as compared to the pretreatment except Patient C, had achieved a complete hematological response (range 5-86 months) after initiating treatment with IFN-α. 

Discontinuation of IFN-α and Thiamazol treatment.

At the time of diagnosis of thyroid dysfunction, all patients, except Patient C, had a slightly elevated anti TPO level at 76 U/ml. Thyroid peroxidase antibodies (anti TPO), were not regularly measured, except for Patient F, who had a slightly elevated anti TPO level at 76 U/ml.

Six patients developed hypothyroidism (Patient A, B, C, F, G and H) and 2 developed hyperthyroidism (Patient D and E) (Table 1). Patient D developed hyperthyroidism during the initial treatment with IFN-α and subsequently hypothyroidism when IFN-α was reinstituted. Thyroid disease was diagnosed median 10.6 months (range 5-86 months) after initiating treatment with IFN-α.

At the time of diagnosis of thyroid dysfunction, all patients, except Patient C, had achieved a complete hematological response (data not shown). Patient C displayed only minor response as assessed by a decrease in hemoglobin from 16.4 to 15.6 g/dl, but otherwise virtually unchanged cell counts as compared to the pretreatment values. The 7 patients developing hypothyroidism had elevated TSH levels from 4.5 to 100 mU/l (Table 1). All patients had elevated levels of anti TPO, from rather low (191 U/ml, Patient C) to extremely high (21400 U/ml, Patient A) and thereby developed autoimmune thyroid disease (AITD). Thyroglobulin antibodies (anti TG) were only analyzed in one patient (B) being elevated 30 times above normal.

Table 1: Clinical data of eight patients with myeloproliferative neoplasia developing thyroid disease during therapy with interferon-α.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis/age at study period</th>
<th>MPN diagnosis/time of debut</th>
<th>Interferon type</th>
<th>Exposure to IFN (months) before thyroid diagnosis</th>
<th>Last measured normal level of TSH (months prior to thyroid diagnose)</th>
<th>TSH (0.3-4.50 mU/I)</th>
<th>Thyroid disease</th>
<th>Change</th>
<th>Anti-TPO (&lt;30U/ml)</th>
<th>IFN after thyroid disease</th>
<th>IFN status by 2 year follow up</th>
<th>Mutation level (% JAK2 V617F)</th>
<th>Time of MPN diagnosis</th>
<th>Thyroid disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F / 38 41</td>
<td>PV/11.2010</td>
<td>IFN-α2a + 2b</td>
<td>10</td>
<td>2,2 (5)</td>
<td>5,36</td>
<td>20.7</td>
<td>0.006</td>
<td>3000</td>
<td>Continued + Ektrozin</td>
<td>Continued + Ektrozin</td>
<td>1,8</td>
<td>25%</td>
<td>53%</td>
</tr>
<tr>
<td>B</td>
<td>F / 46 52</td>
<td>PV/05.2007</td>
<td>IFN-α2a</td>
<td>15</td>
<td>No data</td>
<td>2.1</td>
<td>7,6</td>
<td>1,8</td>
<td>1950</td>
<td>Continued + Ektrozin</td>
<td>Continued + Ektrozin</td>
<td>7.33</td>
<td>35%</td>
<td>14%</td>
</tr>
<tr>
<td>C</td>
<td>F / 46 48</td>
<td>PV/03.2011</td>
<td>IFN-α2a + 2b</td>
<td>11</td>
<td>No data</td>
<td>1.8</td>
<td>7.6</td>
<td>0.6</td>
<td>2300</td>
<td>Stopped + Thiamazol</td>
<td>Continued + Ektrozin</td>
<td>4.83</td>
<td>46%</td>
<td>8%</td>
</tr>
<tr>
<td>D</td>
<td>F / 41 46</td>
<td>PV/09.2008</td>
<td>IFN-α2b + 2a</td>
<td>5</td>
<td>No data</td>
<td>0.6</td>
<td>5.0</td>
<td>5</td>
<td>2300</td>
<td>Continued + Ektrozin</td>
<td>Continued + Ektrozin</td>
<td>1.71</td>
<td>25%</td>
<td>1%</td>
</tr>
<tr>
<td>E</td>
<td>F / 51 59</td>
<td>PV/07.2005</td>
<td>IFN-α2b</td>
<td>7</td>
<td>No data</td>
<td>1.94</td>
<td>1.94</td>
<td>No data</td>
<td>5310</td>
<td>Continued + Ektrozin</td>
<td>Continued + Ektrozin</td>
<td>4.53</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>F</td>
<td>F / 54 53</td>
<td>PV/12.2009</td>
<td>IFN-α2b</td>
<td>86</td>
<td>No data</td>
<td>0.3</td>
<td>0.3</td>
<td>No data</td>
<td>1870</td>
<td>Continued + Ektrozin</td>
<td>Continued + Ektrozin</td>
<td>212</td>
<td>8%</td>
<td>02%</td>
</tr>
<tr>
<td>G</td>
<td>M / 24 41</td>
<td>PV/03.1996</td>
<td>IFN-α2b</td>
<td>28</td>
<td>No data</td>
<td>4,33</td>
<td>4,33</td>
<td>No data</td>
<td>2310</td>
<td>Continued + Ektrozin</td>
<td>Continued + Ektrozin</td>
<td>No data</td>
<td>25%</td>
<td>33%</td>
</tr>
<tr>
<td>H</td>
<td>F / 49 54</td>
<td>ET/07.2007</td>
<td>IFN-α2b</td>
<td>No data</td>
<td>No data</td>
<td>7,54</td>
<td>7,54</td>
<td>No data</td>
<td>No data</td>
<td>Continued + Ektrozin</td>
<td>Continued + Ektrozin</td>
<td>No data</td>
<td>05%</td>
<td>01%</td>
</tr>
</tbody>
</table>

1Treatment with Ektrozin and unchanged IFN-α.
23 months after change in IFN-α from 180 ug x 1 per week to 135 ug x 2 per month.
3Stopped IFN-α 2 months prior. Not yet in Eltroxin treatment.
4Discontinuation of IFN-α and Thiamazol treatment.

At the time of diagnosis, five patients (Patient A, B, D, E and H) were euthyroid (Table 1). Patient C and F had marginally elevated thyroid-stimulating hormone (TSH) levels and had biochemically subclinical hypothyroidism at the time of diagnosis of PV. Thyroid peroxidase antibodies (anti TPO) were more commonly not measured, except for Patient F, who had a slightly elevated anti TPO level at 76 U/ml.

At the time of diagnosis of thyroid dysfunction, all patients, except Patient C, had achieved a complete hematological response (data not shown). Patient C displayed only minor response as assessed by a decrease in hemoglobin from 16.4 to 15.6 g/dl, but otherwise virtually unchanged cell counts as compared to the pretreatment values. The 7 patients developing hypothyroidism had elevated TSH levels from 4.5 to 100 mU/l (Table 1). All patients had elevated levels of anti TPO, from rather low (191 U/ml, Patient C) to extremely high (21400 U/ml, Patient A) and thereby developed autoimmune thyroid disease (AITD). Thyroglobulin antibodies (anti TG) were only analyzed in one patient (B) being elevated 30 times above normal. Patient E with hyperthyroidism had no elevated levels of TSH receptor antibodies. At the time of diagnosis of the thyroid disease, patients with hyperthyroidism experienced symptoms such as internal restlessness, tenderness of the thyroid gland, difficulty breathing and palpitations. Patients with hypothyroidism had symptoms such as fatigue, weigh gain, obstipation, periorbital edema and depression.

Patients A, D, E, F, G and H continued the treatment despite having developed thyroid disease and by the last journal review (June 2015), six patients were still treated with IFN-α (Table 1). Patient B has stopped treatment with IFN-α for more than 4 years due to the continuous and marked reduction in the JAK2V617F-allele burden.

In the 2 year follow up, all eight patients had normalized thyroid parameters. Patient B did not receive substitution therapy and normalized TSH upon cessation of IFN-α (Table 1).

In the study period none of the index patients progressed to myelofibrosis, myelodysplasia or leukemia. Two of the patients had subclinical hypothyroidism, but none of the patients were otherwise predisposed to thyroid disease. Four patients (Patient B, C, E and G) were predisposed to autoimmune diseases, and three had autoimmune diseases (Patient C, E and G), including pernicious anemia, celiac...
disease/diabetes mellitus (data not shown).

Discussion

The eight patients reported in this study all developed thyroid disease with positive TPO antibodies during treatment with IFN-α. Seven of the patients were females, and all were treated exclusively with pegylated IFN-α (Table 1). Normalization of thyroid function was observed without any thyroid treatment in two patients after decreasing IFN-α dosage or cessation of IFN-α. These results support the contention of the AITD, being likely induced by IFN-α [15]. Our results corroborate a previous report that some 10% of MPN patients are prone to develop thyroid disease during non-pegylated IFN-α, including biphasic courses [16]. Importantly, autoimmune abnormalities have been described as complications to treatment with IFN-α in MPNs from asymptomatic autoantibodies to symptomatic autoimmune diseases [8].

Thyroid dysfunction has been reported to be frequent in patients with hepatitis C during treatment with IFN-α [2,13,14], in particular in female patients and increasing with age [16,17]. Of note, in our series of patients females were prevalent in accordance with the general observation of a six times increased risk of AITD in women than in men [15].

IFN-α is known to produce autoantibodies and can lead to thyroid disease [17]. Almost all patients with AITD have measurable concentrations of antibodies against TPO and/or TG [15,16], and anti-TPOs were demonstrated in all our patients (Table 1). IFN-α induced thyroid dysfunction is associated with symptomatic disease in only about 3% of the patients, whereas an abnormal TSH level is recorded in up to 20% of the IFN-α treated [12,14]. As also seen in some of our patients the thyroid abnormalities may disappear after cessation of IFN-α [16].

In our study, six patients were euthyroid and two patients had subclinical hypothyroidism before treatment was initiated (Table 1). Positive autoantibodies were only measured in one patient before treatment. These results do not allow to unravel whether or not an abnormal TSH level increases the risk of thyroid disease after initiation of IFN-α treatment. An abnormal TSH level may be due to latent autoimmune disease, and IFN-α may accelerate thyroid dysfunction in a subset of predisposed patients [12,16]. IFN-α treatment in hepatitis C has been reported to aggravate thyroid autoimmunity in patients who have a positive pre-treatment test for thyroid autoantibodies, and not inducing AITD in patients with negative autoantibodies [12]. These data suggest that treatment with IFN-α can lead to different types of AITD, such as Graves’s disease, hyperthyroidism and hypothyroidism [12,17].

The patients in our study had received IFN-α for 10.6 months (median) before developing thyroid disease, but with a wide range (Table 1). A trend has been observed towards more frequent development of autoimmunity in female patients, receiving IFN-α in longer periods and for more than one year in patients with hepatitis C, and may be dose dependent [18]. A female predominance was recorded in our patients, confirming results in a previous study in MPN patients being treated with non-pegylated IFN [10], although less frequent than in IFN-α treated patients with hepatitis C [14].

It is important to note that AITH was observed predominantly in patients with PV. The patients were also younger (43 years) (Table 1) than the average age at debut of the disease (60 years) and showing a female preponderance [19]. The younger age likely reflects that IFN-α is administered mostly to young patients with MPN, but the age at the study period (Table 1) still is lower than in the cohort (50 versus 56 years-old). The age-distribution of the cohort also reflects that pegylated IFN-α2 may indeed be administered to patients above 60 years-old [7,9]. Interestingly, in our study only one patient with ET treated with IFN-α were observed to develop AITD. Further studies are needed to clarify if patients in the very early cancer stage - ET - may be less prone to develop autoimmune phenomena/diseases during treatment with IFN-α.

In some of the patients in our study, fatigue was reported as a side effect to treatment with IFN-α. Some symptoms such as hair loss, fatigue, weight loss or gain and mental changes can be signs of a thyroid disease, but at the same time also be side effects to treatment with IFN-α [5,8]. Thus, these symptoms can be misinterpreted as side effects, even though they may also be the first symptoms of an evolving or persistent thyroid disease.

The mutation burden during treatment with IFN-α was reduced in all JAK2-positive patients (Table 1). A sustained remission with very low JAK2 allele burden (< 0.3%) was recorded in one patient, who has now been observed for four years after discontinuation of treatment with IFN-α. In advanced stages of malignant melanoma treated with IFN-α, some patients developed autoimmune diseases, including thyroid disease. Highly interesting, autoimmune disease was associated with an increased life expectancy [20]. The hypothesis was that a robust antitumor defense may increase the survival, but also lead to autoimmunity. In patients with chronic myeloid leukemia (CML) treated with IFN-α, the risk of autoimmune diseases has been shown to be increased. Importantly, the subset of CML patients with concurrent autoimmune diseases also displayed a significantly higher probability of obtaining a cytogenetic remission [21]. This beneficial effect has been explained by an increased anti-tumor effect, reflecting a solid immune defense system against malignant cells, but also auto antigens.

In conclusion, our study in MPN supports the hypotheses that IFN-α may trigger AITD in at least 5% of the patients. The results highlight the importance of assessing thyroid function (TSH) prior to initiating IFN-α and monitoring thyroid function during treatment with pegylated IFN-α in MPN - in particular within the first year in female patients. These measures are of particular importance in those patients, displaying abnormal TSH values or positive TPO antibodies before IFN-α treatment, in patients with autoimmune diseases, and in younger women with PV. Patients suffering from fatigue, depression or obstubition should be examined for AITD to differentiate these symptoms as IFN-α side effects, from symptoms related to the MPN or other causes. The follow-up of our patients shows that continuation of IFN-α treatment is safe in patients developing hypothyroidism, when substitution therapy for myxedema is adequately addressed. In patients developing thyrotoxicosis, discontinuation of IFN-α treatment is recommended until hyperthyroidism is well-controlled.

Conflicts of interest

Dr. Ole Weis Bjerrum reports personal fees from Novartis, personal fees from Bristol-Myers Squibb, personal fees from Pfizer, outside the submitted work.

This manuscript titled “Autoimmune thyroid disease in patients with Philadelphia-negative chronic myeloproliferative neoplasms treated with interferon-alpha” originates from the Hematology departments of two University Hospitals in the Copenhagen area, Roskilde and Rigshospitalet.


