

# Imatinib Therapy in Chronic Myelogenous Leukemia and Thyroid Function Tests

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## ABSTRACT

**Introduction:** Imatinib, a tyrosine kinase inhibitor which resulted in much improvement in the treatment of chronic myelogenous leukemia (CML), may adversely affect thyroid gland function. To date, assessment of thyroid function during imatinib therapy has limited to retrospective studies. The aim of this study was to evaluate the effects of imatinib on thyroid function in a prospective manner.

**Materials and Methods:** In this prospective study, 16 newly diagnosed adult subjects with positive Philadelphia chromosome in chronic phase of CML without any other apparent underlying diseases were enrolled. Free T3, Free T4, TSH, Anti TPO and Anti thyroglobulin antibodies were measured before and after 4 and 12 weeks of treatment.

**Results:** Of the 16 patients, 9 were male (57.1%) and 7(42.9%) were female with a mean age of 29±5 years. There were statistically significant changes within reference ranges in serum concentrations of TSH (P=0.753 and 0.002), Free T3 (P=0.012 and 0.007) and Anti Thyroglobulin (P=0.221 and 0.041) 1 month before and 3 months after imatinib initiation, respectively. At the same time, there were no significant changes in serum Free T4 (P=0.196 and 0.650) and Anti TPO (P=0.807 and 0.600) concentrations.

**Conclusion:** This study showed some significant changes on thyroid function tests during imatinib therapy. However, all of them were within the normal range without any clinical abnormalities in the course of treatment. We recommend other studies with larger sample size and longer duration of follow-up.

**KEYWORDS:** Imatinib mesylate, Chronic myelogenous leukemia, Thyroid function tests

## INTRODUCTION

Imatinib mesylate, a tyrosine kinase inhibitor, is a targeted therapy for chronic myelogenous leukemia (CML).<sup>1</sup> Its function is related to inhibition of multiple tyrosine kinases such as Bcr- Abl, Platelet-derived growth factor and C kit.<sup>2</sup> Several side effects have been ascribed to imatinib; of them the most common is peripheral edema.<sup>3-6</sup> Tyrosine kinase inhibitors were shown to cause not only thyroid dysfunction in some cases<sup>7</sup> but also may increase the levothyroxine dose in thyroidectomized patients.<sup>8</sup> However, these findings are mostly based on retrospective studies. Here, we assessed the

effects of imatinib therapy on thyroid function tests in a prospective manner.

## MATERIALS AND METHODS

16 (9 male and 7 female) newly diagnosed cases of Philadelphia chromosome positive CML in chronic phase were recruited in this prospective study. Patients receiving medications that may affect thyroid function including steroids, anticonvulsants e.g. phenytoin, iodine and iodine containing drugs, rifampin and salicylates were excluded from the study. Those with any previous thyroid disorders, hepatic dysfunction, renal

dysfunction and any other major systemic illnesses as well as acute and chronic infections were also excluded.

Physical examination including careful thyroid examination was performed at each visit and 5cc of whole blood was obtained from all eligible patients. Sera were stored at  $-80^{\circ}\text{C}$  until further analysis. Imatinib was prescribed at 300 mg/day and patients were evaluated at 4 and 12 weeks after treatment. TSH, Free T4, Free T3, Anti thyroid peroxidase (Anti TPO), and Anti thyroglobulin (Anti Tg) were measured by Chemiluminescence assay (CLIA) just before and after 4 and 12 weeks after initiation of treatment.

Statistical analyses were performed using SPSS software, version 18. Data presented as the mean $\pm$ SE and Wilcoxon signed- rank test was used to compare related parameters with baseline at various times.

The study protocol was approved by local medical ethics committee and informed consent was obtained from all of the participants.

## RESULTS

In this prospective study, 16 eligible patients with newly diagnosed CML and a mean age of  $29\pm 5$  years were enrolled. 9 cases were male (57.1%) and 7 cases were female (42.9%). Changes in thyroid function tests were compared with baseline at 4 and 12 weeks after imatinib therapy. There was statistically significant decrease in TSH level ( $P=0.002$ ) at week 12 (Fig 1) and significant increase in Free T3 at week 4 ( $P=0.012$ ) and 12 ( $P=0.007$ ) (Fig 2) (Table 1). There were no significant changes in

FT4 ( $P=0.650$ ) and Anti TPO ( $P=0.600$ ) during 12 weeks of treatment with imatinib (Table 1).

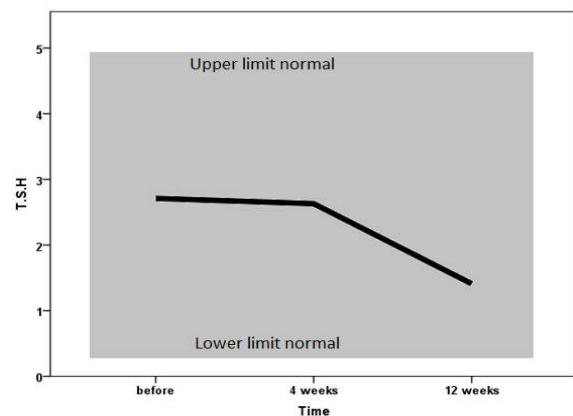


Fig 1: TSH level at 0, 4 & 12 weeks after imatinib therapy

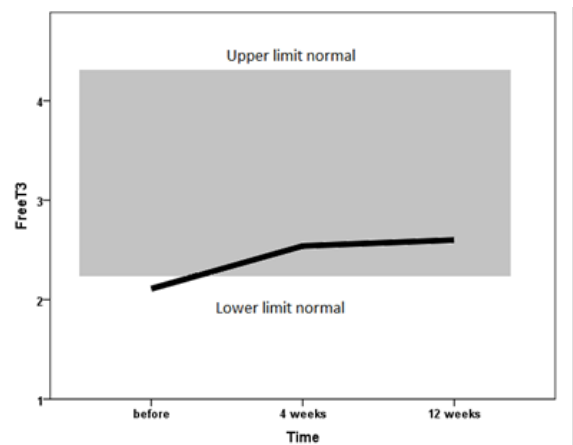


Fig 2: Free T3 changes during 12 weeks of imatinib therapy

Table 1: Baseline parameters & changes during imatinib therapy

Parameter	0 week	4 weeks	P-value	12 weeks	P-value
TSH mlu/L	2.13 $\pm$ 0.40	2.25 $\pm$ 0.70	0.75	1.42 $\pm$ 0.35	0.002
Free T4 pg/ml	1.01 $\pm$ 0.06	1.04 $\pm$ 0.07	0.19	1.03 $\pm$ 0.05	0.65
Free T3 pg/ml	2.10 $\pm$ 0.14	2.58 $\pm$ 0.10	0.012	2.67 $\pm$ 0.10	0.007
Anti TPO IU/ml	11.3 $\pm$ 7.2	15.3 $\pm$ 11.3	0.80	13.5 $\pm$ 9.4	0.60
Anti TG IU/ml	22.8 $\pm$ 10.9	22.5 $\pm$ 12.2	0.221	18.7 $\pm$ 8.70	0.041

## DISCUSSION

Although our results showed statistically significant changes in TSH, FT4 and anti-thyroglobulin during study period, these changes

were within normal laboratory values. In addition, none of the patients clinically developed signs of thyroid dysfunction which further denotes these alterations are not clinically important.

In a similar study by Dora et al., in 2008, all of the cases of CML on imatinib therapy followed for more than six months, none of them developed thyroid dysfunction.<sup>9</sup> In that study, levels of TSH, Free T3, Free T4, Anti TPO, before and during imatinib therapy were normal. However, Degroot et al., in 2005 showed 59% and 63% changes in FT4 and FT3 in patients with thyroid cancer who received imatinib.<sup>8</sup> In another study, imatinib therapy increased dose of levothyroxine in patients with replacement therapy.<sup>10</sup> Kim et al., also reported alterations in thyroid function tests in 25% of patients received imatinib.<sup>11</sup>

More studies were assessed the effects of other tyrosine kinase inhibitors, especially sunitinib on thyroid function. The abnormalities included autoimmune thyroiditis, transient or permanent hypothyroidism and increased dose of levothyroxine.<sup>5, 11-14</sup>

The mechanism of action of tyrosine kinase inhibitors on thyroid was attributed to induction of apoptosis which first manifests as a destructive thyroiditis and then gradually progresses to atrophic hypothyroidism.<sup>5, 15</sup>

Although the sample size was a limiting factor in our study, we followed the patients prospectively for more than 12 weeks. This period of follow-up probably suffices to cover the small sample size.

## CONCLUSION

In contrast to other tyrosine kinase inhibitors, imatinib is not associated with significant clinical adverse effects on thyroid function at least in short-term follow-up.

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## CONFLICT OF INTEREST

All authors declare no conflict of interest.

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