Biology and Medicine

Azimi, Biol Med (Aligarh) 2016, 8:4
http://dx.doi.org/10.4172/0974-8369.1000293

Hypothesis Open Access

# Pentoxifylline Explores New Horizons in Treatment of Hashimoto Thyroiditis

**Arsalan Azimi***

*Doctor of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*

***Corresponding author:** Arsalan Azimi, Doctor of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran, Tel: +989171066597; E-mail: arsalan.azimi@gmail.com

**Received date:** February 01, 2016; **Accepted date:** February 20, 2016; **Published date:** February 25, 2016



**Abstract**

Hashimoto Thyroiditis is an autoimmune disease and the most common cause of hypothyroidism in developed countries. As the disease initiates unusual thyroidal antigens are exposed to the immune system. The immune system sensitizes to those antigens and creates a cell mediated autoimmune response against thyroid gland. Inflammatory cells infiltrate within thyroid follicles and destruct the follicles by inflicting oxidative stress and inducing apoptosis. The inflammatory process also reduces sensitivity of thyrocytes to Thyroid Stimulating Hormone (TSH). As the disease progresses and the follicles degrade, fibrotic tissue replaces the follicles until the whole gland becomes fibrotic. Pentoxiflline could inhibit autoimmune destruction of thyrocytes, suppress cell mediated immune response against thyroid, decrease oxidative damage to thyrocytes, increase sensitivity of thyrocytes to TSH and hinder fibrotic degeneration of thyroid. Thereby PTX could cure HT and alleviate symptoms of hypothyroidism.

## Introduction

Hashimoto thyroiditis (HT) is an organ specific auto-immune disease characterized by presence of auto-antibodies against thyroid antigens, infiltration of leukocytes within the thyroid follicles and destruction of thyrocytes, with a male/female ratio of 1:10-1:20. [1] In iodine sufficient parts of the world, HT is the most common cause of hypothyroidism [2]. Although previous studies had estimated annual worldwide incidence of Hashimoto thyroiditis as 0.3-1.5 cases per 1000 persons, a newer study has revealed that HT is more frequent than expected and the prevalence of euthyroid/hypothyroid patients with HT appears to be even more than 5% in general population [3-5]. Patients often remain asymptomatic for many years and they develop clinical symptoms of hypothyroidism only after advanced destruction of thyroid follicles [1].

Expression of thyroid-specific auto-antibodies against thyroidal antigens leads to infiltration of immune cells in thyroid follicles. Destruction of thyroid follicles by these immune cells is the main mechanism of pathogenesis in HT [6]. Cellular immunity plays the major role in destruction of thyrocytes [7]. HT is a Th1 mediated autoimmune disease and cytotoxic immune cells destroy thyrocytes by induction of apoptosis [6].

Although HT is a frequent autoimmune disease and the leading cause of hypothyroidism in developed countries, the initial process which triggers the disease sequel is not completely understood [8]. Both genetic and environmental factors play roles in the etiology of the disease [9]. Environmental factors including excessive iodine intake, selenium deficiency, pollutants such as tobacco smoke, some infectious diseases, and certain drugs could increase the risk of initiation of HT, primarily in genetically predisposed people [10]. Genetic development of HT is related to genes that over-express Interferon gamma (IFN-γ) [11]. As the disease initiates, thyrocytes enter a cytostatic state followed by progressive destruction and impaired regeneration of thyroid gland which could result in hypothyroidism [12].

Oxidative stress also plays an important role in pathogenesis of the disease. Physiologically, synthesis of thyroid hormones inflicts oxidative stress on thyrocytes [13]. Alteration of cellular defense against oxidative stress results in oxidative damage to thyrocytes, initiating aberrant cell apoptosis and necrosis of the cells, which exposes unusual epitopes to immune system [14,15]. The theory is validated as some antioxidants could alleviate pathogenesis of the disease. For instance, 3 month supplementation with Selenium, an antioxidant, is followed by a significant decrease in serum levels of anti-TPO in patients with HT [16-20]. Selenium is a trace element with multiple tasks within the body and it is also a major component of seleno-enzymes [20], which act in metabolism of thyroid hormones and cellular defense against oxidative stress [18]. Selenium supplementation reinforces intra-thyroidal seleno-enzymes, boosts cellular defense against oxidative damage, modulates production of reactive oxygen species and regulates metabolism of thyroid hormones [18].

Pentoxifylline (PTX) is a methylxanthine derivative with chemical name of 1-5-oxohexyl-3,7-dimethylxanthine [21]. It is shown to reduce ischemia-reperfusion induced damage, inactivate superoxide anions, improve endothelial function and vasodilatation, increase erythrocyte flexibility, attenuate inflammatory reactions, reduce viscosity of blood and inhibit platelet aggregation [21,22]. FDA has approved the agent to treat symptoms of intermittent claudication resulting from peripheral arterial disease [23]. It has also been used to treat Glomerular proteinuric nephropathy, Multi-infarct dementia, Peyronie's disease, Sarcoidosis, Peripheral neuropathy, Sickle cell disease, Alcoholic and non-alcoholic steato-hepatitis, Endometriosis and Radiation-induced fibrosis [24-34].

Gathering the current knowledge together, herein it is hypothesized that PTX can be used as a treatment regime for HT with the goal of remission of the disease but not palliation of disease symptoms.

## Hypothesis

It is hypothesized that PTX may alleviate autoimmune destruction of thyroid gland, it may ameliorates symptoms of HT and it is possible to exert curative effects on HT. Herein, we have gathered the current knowledge together to conclude a uniform pathophysiological mechanism for HT. Thus, based upon the mentioned mechanism involved in the disease, we have suggested a medication (Pentoxifylline) that can alter the pathologic state of the disease in order to prevent both the development and progression of its process. In addition to the main hypothesis, several other relevant hypotheses are also implied.

PTX may decelerate cell-mediated auto immune destruction of thyrocytes during HT.

PTX could increase sensitivity of thyrocytes to TSH and it could facilitate regeneration and redevelopment of thyroid tissue in response to TSH.

PTX could decrease switching of Th17 cells toward Th1cells.

PTX could decelerate infiltration of leukocytes through thyroid follicles during HT.

PTX could ameliorate and attenuate adverse effects oxidative stress in initiation process and during the course of HT.

PTX could ameliorate attenuated effects of TSH on thyrocytes, during HT.

PTX could decrease and/or postpone fibrosis of thyroid gland during Hashimoto thyroiditis [35-39].

These hypotheses could be subjected to several clinical trials to evaluate the efficacy of this medication and compare it with current managements. To evaluate possible curative effects of the medication on the course of HT, PTX should be administered together with Levothyroxine and the patients should be followed by serum level of Anti-thyroid peroxidase antibody (Anti-TPO), Anti-thyroglobulin antibody (ATG) and TSH (Thyroid Stimulating Hormone). As it is expected by the hypothesis, a while after beginning of treatment with PTX, serum level of Anti-TPO and ATG would decrease and finally serum levels of Anti-TPO and ATG becomes near to normal. Then Levothyroxine should be tapered off; thereafter serum levels of TSH are expected to rise. This favors regeneration of the gland under influence of TSH. Finally upon the improvement of function of the gland, as serum levels of TSH normalizes again, PTX could be tapered off. After that, patients should be followed by TSH, Anti-TPO and ATG. Supplementation with Selenium all over this period could facilitate function and regeneration of thyroid gland. In order to evaluate the other minor hypotheses the patients could be followed with serial measurement of serum TSH, serial tissue biopsy and serial counting of Th17 cells.

## Evaluation of Hypothesis

Increased vulnerability to oxidative stress, abnormal immune regulation, autoimmune destruction of thyroid gland, insensitivity to TSH and fibrosis of thyroid gland are found to be the major mechanisms of pathogenesis in HT.

For several reasons it is hypothesized that PTX has the potential to cure HT. PTX is an antioxidant and hypothetically it could improve cellular defense of thyrocytes against oxidative stress induced by synthesis of thyroid hormones or inflammation [13]. This may result in lesser rate of aberrant apoptosis of thyrocytes and lesser exposure of thyroid antigens to immune system. Hypothetically Less exposure to immune system could result in less significant immune response against thyroid antigens. In addition, there is a vicious cycle between autoimmune destruction of thyroid and the immune response against the gland. Pentoxifylline attenuates Th1-type immune reactions, so it can attenuate immune response against thyroid, which in turn decreases exposure of thyroid antigens to immune system [21]. As the rate of exposure decreases, the rate of anti-thyroid antibody formation diminishes. Hypothetically, PTX could also decrease infiltration of leukocytes within the thyroid gland. It also modulates many of the cytokines that are imbalanced during the course of the disease [2,7,40-46]. Thereby it is hypothesized that PTX may decelerate autoimmune destruction of thyroid. Resistance of thyrocytes against TSH is another complication of HT [12]. It is also hypothesized that PTX increases sensitivity of thyrocytes to TSH and accelerates regeneration of damaged gland. Finally PTX could decelerate rate of fibrosis of the thyroid which is the final fate of the gland in HT (Figure 1).

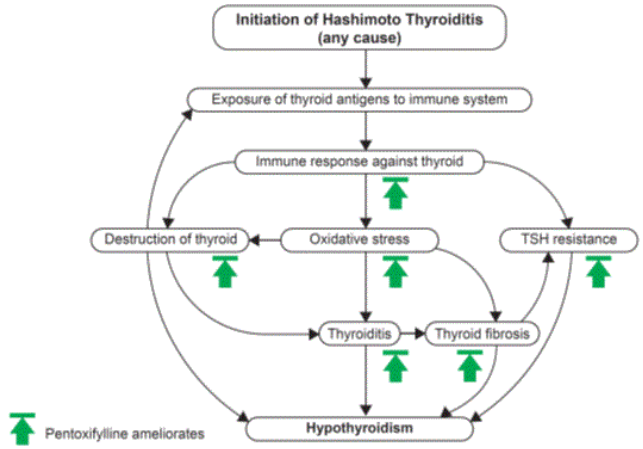


**Figure 1:** The initial processes thattu trigger the sequels of Hashimoto Thyroiditis (HT) are not completely understood, but as the disease initiates unusual thyroidal antigens are exposed to the immune system. The immune system sensitizes to those antigens and creates a cell mediated autoimmune response against thyroid gland. Inflammatory cells infiltrate within thyroid follicles and destruct the follicles by inflicting oxidative stress and inducing apoptosis. The inflammatory process also reduces sensitivity of thyrocytes to Thyroid Stimulating Hormone (TSH). As the disease progresses and the follicles degrade, fibrotic tissue replaces the follicles until the whole gland becomes fibrotic. Pentoxiflline (PTX) could inhibit autoimmune destruction of thyrocytes, suppress cell mediated immune response against thyroid, decrease oxidative damage to thyrocytes, increase sensitivity of thyrocytes to TSH and hinder fibrotic degeneration of thyroid. Thereby PTX could cure HT and alleviate symptoms of hypothyroidism.

### PTX as an immunomodulator

HT is a T-helper type 1(Th1) mediated autoimmune disease and in camparison with T-helper type 2 (Th2) mediated immune reactions; Th1 plays the major role in pathogenesis of the disease [6]. HT is

initiated secondary to Th1/Th2 imbalance [6]. Pentoxifylline equilibrates Th1/Th2 imbalance and attenuates Th1-mediated immune reactions [21,35]. Thereby it is hypothesized that PTX could decelerate cell-mediated autoimmune destruction of thyrocytes in HT.

Lymphocytes infiltrated within the thyroid excrete higher levels of Tumor necrosis factor-alpha (TNF-α), Interferon gamma (IFN-γ), interleukin -1α (IL-1α) and interleukin -1 β (IL-1β), which stimulates the thyrocytes to express and excrete interleukin-6 (IL-6) [37-40]. TNF-α, IFN-γ and IL-1β are all major cytokines that induce apoptosis of thyrocytes via Tumor necrosis factor related apoptosis inducing Ligand (TRAIL)-induced-apoptosis-pathway [7]. PTX down-regulates expression of IFN-γ, IL-1α, IL-1β, IL6, IL-8 and TNF-α, which are all up-regulated during HT [36-41]. In addition, PTX increases production and release of IL-10 which is shown to have curative effects on Hashimoto thyroiditis [40,42]. Human IL-10 interferes with cellular immunity in several fashions; not only it inhibits further expression of IFN-γ by T cells, but it also down-regulates expression of other cell-mediated-immunity related cytokines such as IL-1, IL-2,TNF-α, IL-6 and IL-8 [2,42-46]. As mentioned before, cellular immunity plays the major role in destruction of thyrocytes in HT [7]. As PTX increases production and release of IL-10, and it also reduces production of IFN-γ, IL-1α, IL-1β, IL-2, IL6, IL-8 and TNF-α [2,40-46], it is hypothesized that PTX may decelerate cell-mediated auto immune destruction of thyrocytes during HT.

Over-expression of IFN-γ plays an important role in the initiation of the disease [47]. It has been shown that exogenous administration of IFN-γ induces an organ specific auto-immune thyroiditis with presence of anti-thyroglobulin and anti-microsomal antibodies [47]. In addition over-expression of IFN-γ suppresses secretion of thyroid hormones from thyrocytes, since IFN-γ inhibits functional and morphological response of human thyrocytes to Thyroid Stimulating Hormone (TSH) [12,48]. IFN-γ Induces aberrant expression of MHC-II antigens by thyrocytes [49]. Thyroid cell class II antigens participate in activation and amplification of T cell responses [12,48]. This process leads to further release of inflammatory cytokines including IFN-γ and constitutes a vicious cycle [12,48]. Since PTX down regulates expression of IFN-γ, it is hypothesized that PTX unsettles the vicious cycle. As previously mentioned, IFN-γ inhibits functional and morphological response of human thyrocytes to TSH [12,48]. Thus it is hypothesized that by down-regulating this cytokine, PTX could also increase sensitivity of thyrocytes to TSH and it could facilitate regeneration and redevelopment of thyroid tissue in response to TSH.

In animal models of autoimmune thyroiditis, Interleukin 12 (IL-12) has been demonstrated to be another initiator of Th-1 mediated response against thyrocytes [50]. Considering the issue that IL-12 induces further expression of IFN-γ, IL-12 can be the primary initiator of the disease process [50,51]. PTX also suppresses IL-12 inducted expression of IFN-γ [51]. Thereby it is hypothesized that PTX counteracts the role of IL-12 in initiation and/or progression of the disease.

Th17 cells have been recently identified as a distinct T helper cell lineage and found to play important roles in inflammation and autoimmune diseases. It is shown that intra-thyroid infiltration of Th17 cells is significantly increased in the course of HT [52]. Generation of Th17 cells in humans requires IL-1β and IL-6 with IL-2 as a survival factor [53,54]. In presence of IL-12, Th17 cells also express and secrete IFN-γ [55-57]. In addition IL-12, shifts Th17 cells toward switching intoTh1 cells [58]. As previously mentioned, PTX down regulates IL-1β, IL-6 and IL-2, so it is hypothesized that PTX alters generation and survival of Th17-cells. Furthermore, PTX inhibits production of IL-12 [59]. Therefore it is hypothesized that PTX could decrease switching of Th17 cells toward Th1cells, which are considered to play an important role in the pathogenesis of HT.

PTX also inhibits expression of Inter-Cellular Adhesion Molecle-1 (ICAM-1) on surface of stimulated mononuclear cells, which impairs their migration and infiltration [60,61]. Thereby it is hypothesized that PTX could decelerate infiltration of leukocytes through thyroid follicles.

## PTX as an antioxidant

Previous studies have revealed that Selenium supplementation in patients with HT is followed by a significant decrease in anti-TPO levels [18-20]. Reinforcement of thyroid seleno-enzymes by Selenium is followed by modulation of oxidative stress and regulation of apoptosis [18-20]. It is hypothesized that by modulation of oxidative stress and apoptosis, unusual thyroidal epitopes are not formed and the immune system is no longer exposed to these aberrant self-antigens and as a result, formation of auto-antibodies is regressed. Hypothetically, this exposure could play an important role in initiation of autoimmune thyroiditis, thus using antioxidants which augment cellular defense against oxidative stress, could attenuate the destruction of thyrocytes. It is hypothesized that PTX could do so, since it is an anti-oxidant agent. 8-oxopentoxifylline, one of Pentoxifylline metabolites, is a potent antioxidant and free radical scavenger, which alleviates oxidative damage and strengthens cellular defense against oxidative stress [21]. Thereby it is hypothesized that PTX ameliorates and attenuates adverse effects oxidative stress in initiation process and during the course of HT.

## PTX as a TSH sensitizer

It is also hypothesized that PTX could improve the effects of TSH on thyrocytes. Two main mechanisms are postulated. As previously mentioned, IFN-γ inhibits functional and morphological response of human thyrocytes to TSH [12,48]. As previously mentioned, PTX down-regulates expression of IFN-γ. Thereby it is hypothesized that PTX could reduce the resistance of thyrocytes to TSH. On the other hand, as it is well known, classical human TSH signal transduction pathway includes cAMP as a secondary messenger. As a non-selective phosphodiesterase inhibitor, Pentoxifylline increases the amount of intracellular cAMP [62]. The same as TSH, FSH signal transduction highly depends on amounts of intracellular cAMP and it is shown that PTX boosts and improves the effects of FSH on male germinal cells [20]. As PTX increases the sensitivity to FSH, considering the issue that TSH and FSH are structurally similar to each other, it is hypothesized that PTX may do the same about TSH and thyrocytes. Indeed, it is hypothesized that PTX could ameliorate attenuated effects of TSH on thyrocytes, during HT.

## PTX as an anti-fibrotic agent

As the disease progresses and the follicles degrade, fibrotic tissue replaces thyroid follicles and the disease process continues until the whole gland becomes fibrotic [63-67]. TGF-β is a growth factor essential for tissue repair and also the main cause of tissue fibrosis [64]. Expression of TGF-β is up regulated by IL-1β [66]. PTX down regulates expression of both IL-1β and TGF-β and it is shown to decrease collagen synthesis and fibrosis of human peritoneum

[40,41,65]. Thus it is hypothesized that PTX could decrease fibrosis of thyroid gland during Hashimoto thyroiditis.

## Discussion

HT is the most common cause of hypothyroidism in iodine sufficient parts of the world and it is routinely treated by replacement of thyroid hormones, most commonly Levothyroxine [2,5]. Current treatment is not a remission but only symptomatic, therapy. Prescription of the drug is not as simple as it may seem [68]. Different individuals may need different amounts of hormone replacement, and even one individual may not always require invariable amounts of the drug, because the need for amount of hormonal replacement depends on individuals' metabolic, physical and mental status [68]. In addition as the disease has a progressive course in most of the cases, so the demand for hormonal replacement increases as the thyroid function deteriorates [69-72]. Conversely as the patients with hypothyroidism become older, their demand for hormone replacement decreases and older individuals are at higher risk for overtreatment and iatrogenic thyrotoxicosis and over-replacement with levothyroxine could complicate the patients with osteoporosis and adverse cardiac events, especially atrial fibrillation [69-72]. Furthermore, the same doses of Levothyroxin manufactured by different incorporations do not necessarily result in similar responses in an individual [73]. These all further complicates adjustment of dose of the drug. Many of HT patients need the drug lifelong as their disease does not remit spontaneously [71]. Although Levothyroxine is a relatively available and inexpensive drug, since it is needed for a long period of time, the total cost of medication per patient would be significantly high [71]. In addition HT patients and TSH levels should be screened every 6-12 months, which further increases the total cost of treatment of the disease [71,73]. Considering the increased risk of papillary carcinoma of thyroid in persistence of HT [1] beside difficulties in dose adjustment of Levothyroxine, possible complications of over-treatment and significant total costs expended upon this symptomatic therapy, it is not irrational to think of an alternative treatment to cure the disease, but not palliation of its symptoms.

Here it is hypothesized that PTX could be an alternative therapy for HT. Although in comparison with Levothyroxine, PTX is a relatively expensive and less available drug, but it has tolerable adverse effects and it is a relatively safe drug [74,75].Thereby as PTX has the potential to become an alternative in the treatment of HT and it is not needed to be prescribed lifelong, it is not irrational to put the hypothesis in a trial.

## Conclusion

All clues together, PTX is an anti-inflammatory/anti-oxidant agent and it may reduce inflammation and aberrant apoptosis of thyroid epithelial cells. It may reduce exposure of intra cellular/follicular components to immune system and decrease infiltration of leukocytes within thyroid follicles. It may ameliorate decreased responsiveness of throcytes to TSH. PTX may accelerate regeneration of damaged thyrocytes as it suppresses IFN-γ and up-regulates production of IL-10 and it also inhibits fibrosis of the gland. All in all PTX may have curative effects on HT and may have the potential to become an alternative treatment. Evaluation of the issue with clinical researches and cohort large studies are necessarily needed to validate/invalidate the hypothesis.

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