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THE IMMUNOLOGICAL EFFECT OF TYROSINE INHIBITOR OF A CLEEVEC IN AUTO – IMMUNE THYROID PEROXIDASE

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ABSTRACT: *Imatinib (Gleevec) a tyrosine kinase inhibitor that targets the so-called Philadelphia to chromosome characteristic of chronic myeloid leukemia (CML), was the first yield complete and lasting responses and is now widely used as first-line treatment as the researchers noted. The drug have been widely used in the treatment of several hematological malignancies. It is the frontline therapy of the majority of CML patients. Many patients are treated for long periods, and there is concern about the long-term immune effects of its use. Autoimmune disorders in patients treated with Gleevec drug may be related to the direct immunomodulating properties or may be linked to a possible toxic effect in target organs, triggering autoimmunity. On the other hand, the immune effects of Gleevec may play a role in its therapeutic actions. In this report we describe the development of symptomatic autoimmune thyroid diseases (thyroid peroxidase) in (9.6%) out of 51 patients with age range (16-70) years male and female and with a cure period (8 months to 10 years) in chronic treatment with recombinant a Gleevec drug (400mg) in patients with CML by using Enzyme Linked Immune Assay (ELISA). The patients samples were collected from Iraqi National Center for Research and Treatment of Hematological Diseases/University of Al-Mustansiryiah which were diagnosed for chronic myelogenous leukemia according to physical examination, Real-time PCR technique for detection quantification of mRNA chimerical gene bcr/abl (M-bcr) and mRNA gene/ abl in the clinical material. Epidemiological data such as age, sex and cure period were recorded for all of the patients. The aim of the study was to test the possible association between the generation of autoimmune phenomena on thyroid peroxidase and the effect of gleevec drug.*

KEYWORDS: Chronic Myeloid Leukemia, Autoimmunity Thyroid Diseases

INTRODUCTION

Chronic myeloid leukemia is a clonal myeloproliferative disorder of a pluripotent stem cell (1,2). It was the first malignancy that had a specific chromosomal abnormality uniquely linked to it after the discovery of a minute chromosome now known as the Philadelphia (Ph) chromosome (3) later defined to result from a t(9;22) reciprocal chromosomal translocation(4). Critical importance was the demonstration that this translocation involved the *Abl1* (Abelson) proto oncogene in chromosome 9 and the *BCR* (breakpoint cluster region) gene in chromosome 22(5,6**)**. Patients with CML which create an abnormal gene called Bcr/Abl leads to the production of a type of enzyme called a tyrosine kinase, which signals the marrow to make too many white blood cells. Imatinib works by blocking the tyrosine kinase enzyme so that the marrow stops (slows down) making too many white blood cells. For this reason, imatinib and similar drugs are called tyrosine kinase inhibitors (TKIs) (7,8). With Gleevec, a remarkable cancer drug, the approach was to target the disease at the cellular and subcellular level. Gleevec, also marketed internationally as Gleevec and sometimes referred to by its chemical name

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imatinib, entered the medical world with a bang. Imatinib is a small-molecule protein tyrosine kinase inhibitor developed to target the gene product of the Philadelphia chromosome *Bcr*/*Abl* translocation in chronic myelogenous leukemia (CML). Imatinib was initially approved for the treatment of Bcr/Abl-positive CML and more recently approved to treat c-Kit–expressing gastrointestinal stromal tumors (GISTs) based on its ability to antagonize c-Kit (7,9). Tyrosine kinases (TKs) are important for the regulation of growth, differentiation, survival, and motility of various tumors over express TKs or harbor activating TK mutations leading to uncontrolled mitogenic signals to the neoplastic cells (10, 11, 12, 13, 14, 15). Imatinib mesylate as an example of this novel class of drugs suppresses the TK activities of c-abl, BCR-ABL, platelet-derived growth factor receptor (PDGFR), and c-kit receptors Gleevec has also been approved for use in patients with several types of gastrointestinal tumors, can provide benefit in autoimmune arthritis but has not been previously determined. (16, 17, 18, 19, 20, 21). The imatinibe have many properties in many immunity cases:

It inhibits macrophage signal transduction events**,** M-CSF is present in RA synovial tissue and has been shown to exacerbate CIA , inhibits TNF-α production by human RA SFMCs, inhibits: mast cell production of proinflammatory cytokines, B cell proliferation and immunoglobulin production in vitro, anti-collagen T cell proliferation and cytokine production are inhibited by imatinib (22, 23, 24, 25, 26).

METHODOLOGY

The samples of fifty one patients male to female (49.02% to 50.98%) range age (16-70) were carried out and diagnosed by the consultant medical staff at the National Centre of Haematology of Al-Mustansiryiah University. The diagnosis was based on a clinical examination, laboratory investigations of complete blood picture, histopathological examination of bone marrow aspirate and biopsy. Molecular study was done by (RT – PCR) technique (Sacace kit Biotechnologies) for detection quantification of mRNA chimerical gene bcr/abl (M-bcr) and mRNA gene/ abl in the clinical material by using Gene Expert diagnosis system, and also cytogenetic analysis by using FISH technique. The association of diagnosis tests were confirmed in special privet lab which bonded with Institutes of Baghdad Al-Kahrk Health / Ministry of Iraqi Health. The samples of patients were compared with ten of control group included subjects who were apparently healthy, but they had no signs or symptoms of any type of leukemia, as detected by their diagnosis tests and the consequent view point of the consultant medical staff.

Collection of samples:

Venous blood samples were obtained from CML patients and control subjects. The patients were randomly selected concerning to age, gender, disease duration, disease phase. The blood of 10 ml of samples were collected by venipuncturea, they were drawn into types of tube EDTA and a plain tubes for detection tests as mentioned above. The samples collected by plain tube were subjected to centrifugation after 2000 rpm for 10 minutes to collect sera for the assessment of TPO (Aeskulisa company) by using ELIZA test. The sera were frozen at -20ºC until the assessment.

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Laboratory Investigations

Anti Thyroid Perioxidase a TPO membrane –bound glycoprotein of thyroid gland, autoantibodies to Tg and TPO are important for ruling out autoimmune thyroid diseases, a TPO was detected by ELISA; this assay system utilizes anti-human immunoglobulins conjugated to horse radish perioxidase. The normal range of a TPO as recommended by Aeskulisa is ≤ 40 IU/ ml.

RESULT AND DISCUSSION

Thyroid dysfunction, is a well recognized side effect of treatment with tyrosine kinase inhibitors (TKIs) (27). Cleevec can cause unusual adverse effects, multitargeted of TKIs that have been demonstrated to induce hypothyroidism and thyroid dysfunction. Retrospective studies indicate that TKIs can induce hypothyroidism (28,29). So as the effectiveness of TKIs on thyroid diseases through an autoimmunity, in which the body's immune response turns against itself. The autoimmune response is triggered by a combination of genetic and environmental factors . The presence of autoantibodies to thyroid peroxidase is an indication of autoimmune thyroid disease. The two most common thyroid autoimmune diseases are Graves disease and Hashimoto thyroiditis, abnormal levels of thyroid hormones and an enlarged thyroid gland (goiter) are features of these disorders. Autoantibodies to thyroid peroxidase are present in about 75 percent of people with Graves disease and 90 percent of those with Hashimoto thyroiditis (30, 31, 32, 33, 34). Thyroid peroxidase antibody positivity is seen in 10–15% of the general population and is not an indication for treatment where there is no biochemical abnormality of thyroid function (35, 36,37).

In our study of 51 Iraqi patients are currently in chronic treatment with a cleevec for hematological malignancies of CML, the median age was 48.06 range (16-70) years, the percent of males to females were (50.98 % to 49.01%) . Thyroid peroxidase are important for ruling out autoimmune thyroid diseases, the normal range of a TPO as recommended by Aeskulisa kit is ≤ 40 IU/ ml as mentioned above. In this report we describe only 5 of these patients (9.6 %) of the total, whom developed a symptomatic autoimmune thyroid peroxidase among the periods of : 8 months, (1.5, 4, 7 and 9) years of cleevec treatment, with their age (42y , 53y , 40y, 52y and 43y) respectively. (35, 36, 37). Thyroid biopsies were not performed to verify the diagnosis because the patterns of thyroid autoantibodies were characteristic. 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 a cleevec, and questions regarding the management of overt thyroid diseases during the treatment itself and the exacerbation of autoimmune diseases during cleveec therapy. The incidence of thyroid diseases varied and the time between start of therapy and development of thyroid disease varied considerably with intervals ranging (38).

These data suggest that at least the presence of anti-thyroid peroxidase must be carefully documented in patients undergoing a cleevec therapy, and that possibly, something other than cleevec 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. Regarding the management of overt thyroid diseases during long-term a-cleveec treatment, a distinction must be made between glandular hyper- or hypofunction. Certain antidepressant may cause hypothyroidism,

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although this is rare. Interlukins and interferons are used for treating CML and other conditions increase antibodies that put patient at risk factor hypo or hyperthyroidism, so as some drugs used in cancer chemotherapy such as sunitinib (sunet) or imatinib (cleveec), can also cause thyroid dysfunction. (27).

The mechanism by which clivic induces autoimmune thyroid peroxidase 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 tollerance and induce autoantibody formation and activation of cytotoxic or suppressor T lymphocytes and NK cells. Hyperthyroidsm 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. And hypothyroidisim by thyroid-cell death due to an accumulation of lymphocytes, predominantly T cells, in the thyroid(38) Large granular lymphocytic leukemia is frequently accompanied by autoimmune processes such as rheumatoid arthritis (often manifested as Felty's syndrome) and immune-mediated cytopenias (39). T-cell large granular lymphocytic leukemia was initially described as a clonal disorder of large granular lymphocytes involving blood, bone marrow, spleen, and liver (40). This disorder is characterized by the presence of abnormal CD3+CD8+CD57+ lymphocytes corresponding to activated effector cytotoxic T lymphocytes (CTLs) (41,42). Large granular lymphocytes can secrete several cytokines that may play a role in immune-mediated cytopenias and autoimmune disorders (43, 44).

REFERENCES

Abramson S, Miller RG, Phillips RA. The identification in adult bone marrow of pluripotent and restricted stem cells of the myeloid and lymphoidsystems. *J Exp Med*. 1977;145:1567-1579.

Annavarapu SR, Natalia K, Reinhard VW, Vladimira J, Shashi KT, Julia R, Georg B. () Wnt/_-Catenin Signaling Mediates Antineoplastic Effects of Imatinib Mesylate (Gleevec) in Anaplastic Thyroid Cancer The Journal of Clinical Endocrinology & Metabolism 2006; 91: 159–168

Bartram CR, de Klein A, Hagemeijer A, et al. Translocation of c-ab1 oncogene correlates with the presence of a Philadelphia chromosome in chronic myelocytic leukaemia. *Nature*. 1983;306:277-280.

Benoist, C., Mathis, D. 2002. Mast cells in autoimmune disease. *Nature.* 420:875-878.

Burks EJ, Loughran TP Jr. Pathogenesis of neutropenia in large granular lymphocyte leukemia and Felty syndrome. Blood Rev. 2006;20:245-266.

Burmester GR, Stuhlmuller B, Keyszer G, Kinne RW. Mononuclear phagocytes and rheumatoid synovitis. Mastermind or workhorse in arthritis? *Arthritis Rheum.* 1997; 40:5-18.

Campbell IK, Rich MJ, Bischof RJ, Hamilton JA. The colony-stimulating factors and collagen-induced arthritis: exacerbation of disease by M-CSF and G-CSF and requirement for endogenous M-CSF. *J. Leukoc. Biol.* 2000; 68:144-150.

Chardès T, Chapal N, Bresson D, Bès C, Giudicelli V, Lefranc MP, Péraldi-Roux S. "The human anti-thyroid peroxidase autoantibody repertoire in Graves' and Hashimoto's autoimmune thyroid diseases". *Immunogenetics* 2002; 54 : 141–57.

Dameshek W. Some speculations on the myeloproliferative syndromes. *Blood*. 1951;6:372-375.

Print ISSN: ISSN 2053-406X, Online ISSN: ISSN 2053-4078

Demetri GD, *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N. Engl. J. Med.* 2002; 347:472-480.

Dewar AL, *et al*.. Macrophage colony-stimulating factor receptor c-fms is a novel target of imatinib. *Blood.* 2005; 105:3127-3132.

Doerge DR, Sheehan DM. "Goitrogenic and estrogenic activity of soy isoflavones". *Environ. Health Perspect*. 110 Suppl. 2002; 3: 349–53.

Druker BJ, *et al*. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N. Engl. J. Med.* 2001; 344:1031-1037.

Eklund KK, Joensuu H. Treatment of rheumatoid arthritis with imatinib mesylate: clinical improvement in three refractory cases. *Ann. Med.* 2003; 35:362-367.

Federico S *et. al.* Development of autoimmune thyroid diseases during long term treatment of heamatological malignancies with interferon- alpha. *Haematologica* 1994; 79:367-370.

Francesco Torino , *et al*. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy Nature Reviews Clinical Oncology 2009; 219-228.

Gordon, J.R., Galli, S.J. 1990. Mast cells as a source of both preformed and immunologically inducible TNF-alpha/cachectin. *Nature*2000; 346:274-276.

Groffen J, Stephenson JR, Heisterkamp N, de Klein A, Bartram CR, Grosveld G. Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. *Cell*. 1984;36:93-99.

Juurikivi A *et al*.. Inhibition of c-kit tyrosine kinase by imatinib mesylate induces apoptosis in mast cells in rheumatoid synovia: a potential approach to the treatment of arthritis. *Ann. Rheum. Dis.* 2005; 64:1126-1131.

Kimura S, Kotani T, McBride OW, Umeki K, Hirai K, Nakayama T, Ohtaki S. "Human thyroid peroxidase: complete cDNA and protein sequence, chromosome mapping, and identification of two alternately spliced mRNAs". *Proc. Natl. Acad. Sci. U.S.A.* 1987; 84: 5555–9.

Kinne RW, Brauer, R, Stuhlmuller, B, Palombo-Kinne, E, Burmester, GR. Macrophages in rheumatoid arthritis. *Arthritis Res*2000*;* 2:189-202.

Kontoyiannis D, Pasparakis M, Pizarro TT, Cominelli F, Kollias, G.. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. *Immunity.* 1999; 10: 387-398.

Loughran TP Jr, Kadin ME, Starkebaum G, *et al*. Leukemia of large granular lymphocytes: association with clonal chromosomal abnormalities and autoimmune neutropenia, thrombocytopenia, and hemolytic anemia. Ann Intern Med 1985;102:169-175

Loughran TP Jr. Clonal diseases of large granular lymphocytes. Blood 1993;82:1-14

Loughran TP Jr. Clonal diseases of large granular lymphocytes. Blood 1993;82:1-14

McLachlan SM, Rapoport B. "Autoimmune response to the thyroid in humans: thyroid peroxidase--the common autoantigenic denominator". *Int. Rev. Immunol.* 2000; 19 : 587–618.

Nowell PC. Discovery of the Philadelphia chromosome: A personal perspective. *Journal of Clinical Investigation* 2007; 117:2033–2035.

Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. *Science*. 1960;132:1497.

O'Leary PC, Feddema PH, Valdo PM, et al. Investigations of thyroid hormones and antibodies based on a community health survey: the Busselton thyroid study. Clin Endocrinol 2006;64:97–104.

Osman GE, *et al*. Expression of a type II collagen-specific TCR transgene accelerates the onset of arthritis in mice. *Int. Immunol.* 1998; 10:1613-1622.

Print ISSN: ISSN 2053-406X, Online ISSN: ISSN 2053-4078

Pixley FJ, Stanley ER. CSF-1 regulation of the wandering macrophage: complexity in action. *Trends Cell Biol.* 2004; 14:628-638.

Preedy VR, Burrow GN, Watson RR, editors. Iodine: nutritional, biochemical, pathological and therapeutic aspects. Oxford: Elsevier, 2009.

Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature*. 1973;243:290-293.

Ruf J, Carayon P. "Structural and functional aspects of thyroid peroxidase". *Arch. Biochem. Biophys.* 2006; 445: 269–77.

Sokol L, Loughran TP Jr. Large granular lymphocyte leukemia. Oncologist 2006;11:263-273

Sokol L, Loughran TP Jr. Large granular lymphocyte leukemia. Oncologist 2006;11:263-273-

Su E J, *et al*. Activation of PDGF-CC by tissue plasminogen activator impairs blood-brain barrier integrity during ischemic stroke. *Nature Medicine*; 2008; 14: 731–737.

Theo D K *et.al*. Thyroid Dysfunction Caused by Second-Generation Tyrosine Kinase Inhibitors in Philadelphia Chromosome-Positive Chronic Myeloid Leukemia. Thyroid 2010

Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 1995; 43:55–68.

Weinblatt ME., *et al*. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N. Engl. J. Med.* 1999; 340: 253-259.

Wolf, AM *et al*. The kinase inhibitor imatinib mesylate inhibits TNF-alpha production in vitro and prevents TNF-dependent acute hepatic inflammation. *Proc. Natl. Acad. Sci. U. S. A.* 2005; 102: 13622-13627.

Wong E, Rosen LS, Mulay M, Vanvugt A, Dinolfo M, Tomoda C, Sugawara M, Hershman JM. Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. Thyroid 2007; 17:351–355.

Woolley DE. 2003. The mast cell in inflammatory arthritis. *N. Engl. J. Med.* 348:1709-1711.

Woolley DE., Tetlow LC. Mast cell activation and its relation to proinflammatory cytokine production in the rheumatoid lesion. *Arthritis Res.* 2:65-74.

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