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## INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/11090  
DOI URL: <http://dx.doi.org/10.21474/IJAR01/11090>



### RESEARCH ARTICLE

#### THE EFFECT OF ETANERCEPT ON BLOOD LIVER ENZYMES IN PATIENTS WITH CHRONIC PLAQUE PSORIASIS

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#### Manuscript Info

##### Manuscript History

Received: 05 April 2020  
Final Accepted: 07 May 2020  
Published: June 2020

##### Key words:-

Psoriasis, Etanercept, Liver Enzyme, TNF-a

#### Abstract

**Background:** Psoriasis is a chronic inflammatory skin disease with an incompletely understood pathogenesis, partly an immune dysfunction. Immunomodulatory agents like biologics drugs are one of the systemic treatments being used. As a side effect, they can cause a form of hepatitis manifested by elevations of the blood liver enzymes.

**Methodology:** A cross-section study of a total of fifty patients with severe chronic plaque psoriasis were treated with the biologic anti-TNF inhibitor agent, Etanercept, and followed up for twenty four months by regular blood liver enzymes estimations

**Results:** Fourteen patients (28%) showed increased enzymes levels, of them five patients (10%) showed elevated alanine aminotransferase and/ or aspartate aminotransferase levels, six patients (12%) showed elevated alkaline phosphatase, and three patients (6%) showed elevated levels of the three enzymes at the same time. It was reported that almost all of them showed an acceptable amount of elevations which were less than two folds of the upper normal level and only two patients (4%) exceeded two folds of the upper normal level.

**Conclusion:** The overall frequency of elevations in blood liver enzymes in our patients was 14 (28%) collectively. The range was from 6-12% according to the type of the enzyme. The onset of blood liver enzyme elevations was from 3 to 24 months after starting the medication.

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#### Introduction:-

Psoriasis is one of the prototypic papulosquamous skin diseases characterised by erythematous papules or plaques with silvery scales. It is a chronic inflammatory skin disease with increased epidermal proliferation related to dysregulation of the immune system<sup>(1)</sup>.

Psoriasis can present at any age and has been reported at birth and in older people of advanced age<sup>(2)</sup>. It has a bimodal age distribution, with peak onsets between 20-30 years and 50-60 years. Psoriasis is fairly common, affecting approximately 2% of the general population<sup>(1)</sup>.

Certain factors may trigger psoriasis such as: Infections, injury to the skin, a bug bite, severe sunburn, stress, smoking, heavy alcohol consumption, vitamin D deficiency and certain medications like lithium, beta blockers, and iodides<sup>(3)</sup>.

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The hallmark of psoriasis pathogenesis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. The histology of the psoriatic plaque shows acanthosis (epidermal hyperplasia), which overlies inflammatory infiltrates composed of dermal dendritic cells, macrophages, T cells, and neutrophils. Neovascularization is also a prominent feature<sup>(4)</sup>.

Plaques can occur anywhere on the skin, but are most common on the elbows, knees and scalp, and often, the trunk and buttocks. Some patients present with a predominant involvement of the palms and soles. Psoriasis may involve the nails as well as the skin. Other forms of psoriasis include an inverse type characterized by erythematous plaques but no visible scaling in the axillae and groins. There is also a pustular type with scattered pustules on the base of markedly erythematous plaques<sup>(5)</sup>.

This condition is associated with high fever; psoriatic arthritis associated with HLA-B27<sup>(5)</sup>. Several patterns of joint involvement, and guttate psoriasis which typically presents after acute streptococcal infection in young adults and is characterized by numerous, small oval-shaped plaques concentrated on the trunk<sup>(6)</sup>.

Commonly used measures for scoring the severity of psoriasis include the Psoriasis Area and Severity Index (PASI), and the Physician Global assessment. Clinicians assess the severity of the disease, taking into account the degree of scaling, redness, thickness of the skin lesions or the size of the BSA occupied by psoriasis. QoL measures are also important<sup>(7)</sup>.

The PASI is a measure of overall psoriasis severity and coverage. The British guidelines define "severe" disease as PASI score of 10 or more<sup>(1)</sup>. A 75% improvement in the PASI score (PASI-75) is predominantly used to document the effectiveness of individual therapies in clinical trials of patients with extensive psoriasis<sup>(8)</sup>. Psoriasis has no cure.

*Etanercept: is a fully soluble, human dimeric fusion protein, functions as a TNF inhibitor by competitively binding to TNF and preventing its activation of the inflammatory cascade. Etanercept is a soluble form of the p75 receptor that inhibits TNF- $\alpha$ , and to some extent TNF- $\beta$ , by blocking its interaction with cell-surface TNF receptors. The dimeric structure of Etanercept allows it to bind TNF at an affinity that is 50 to 1000 times greater than naturally occurring TNF receptors. By binding and sequestering TNF, Etanercept modulates biologic responses involved in the pathogenesis of psoriasis, such as the expression of adhesion molecules that function in leukocyte migration, serum cytokine levels, and serum matrix metalloproteinase-3 levels<sup>(9)</sup>.*

Despite their many benefits, several serious side effects exist and adverse reactions do occur from the use of anti TNF agents. Liver injury although uncommon, has been observed in some patients<sup>(10)</sup>. Drugs can cause liver injury and among the most common causes of drug-induced liver injury (DILI) are TNF- $\alpha$  inhibitors<sup>(11)</sup>. Raised transaminases occurring while patients are taking both anti-TNF drug and methotrexate are difficult to interpret<sup>(12)</sup>.

Liver blood tests can be used to assess liver injury. Among the most sensitive and widely used liver enzymes are the aminotransferases. They include aspartate aminotransferase (AST) is also known as serum glutamic oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT) is also known as serum glutamic pyruvic transaminase (SGPT). However, it must be emphasized that higher-than-normal levels of these liver enzymes should not be automatically equated with liver disease. They may mean liver problems or they may not. Alkaline phosphatase (ALP) is an enzyme found in bones, bile ducts, and liver. High levels of ALP may indicate liver inflammation, blockage of the bile ducts, or a bone disease. Children and adolescents may have elevated levels of ALP because their bones are growing<sup>(13)</sup>.

#### **Aim of the Study:**

This study was carried out in order to have an idea about the effect of the biologic anti-TNF inhibitor drug (Etanercept) on the level of blood liver enzymes during the treatment of patients with severe chronic plaque psoriasis.

#### **Patients and Methods:-**

A total of 50 patients suffering from severe chronic plaque psoriasis with established diagnosis of psoriasis, treated with anti-TNF (Etanercept) at The Department of Dermatology in Al-Yarmouk Teaching Hospital were included in this cross-sectional study. The period of the work extended from February 2017 to February 2020.

All patients were questioned regarding their names, gender, age, address, age of onset of the disease, duration of the disease, seasonal variation of the disease severity, aggravating factors, previous use of topical and systemic anti-psoriatic treatments, alcohol consumption (for adults ) and history of present and past medical problems(especially liver diseases ) and drugs taken for them.

A full clinical examination was then done for all patients to identify the type of the lesions, sites, numbers, extent, and their PASI.

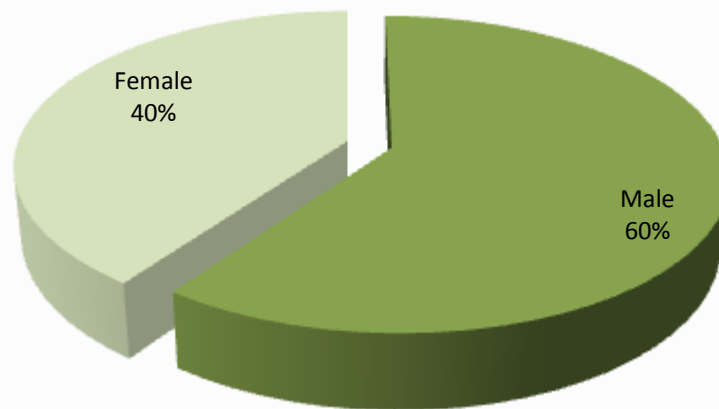
All patients were investigated for complete blood picture, ESR, general urine examination, renal function tests, liver function tests, viral screening (HIV, HBsAg, HCV Ab), skin test for tuberculosis (either tuberculin skin test-TST or interferon gamma release assay blood test-IGRA), and chest x-ray.

Liverenzymes(AST, ALT, and ALP) were done for the patients. These tests were done at the time of beginning of the treatment (baselinetime) and then regularly every three months during the period of the treatment which is up to two years.

All patients were given the anti-TNF agent (Etanercept) in a dose of 50 mg as a subcutaneous injection twice weekly for the adult patients and in a dose of 25 mg subcutaneous injection twice weekly for the children during the first 3 months of treatment. Then the dose was reduced to 50 mg subcutaneous injection once weekly for the adult patients and 25 mg subcutaneous injection once weekly for the children throughout the remaining period of treatment.

### Results:-

A total of 50 patients with severe chronic plaque psoriasis treated with TNF-inhibitor (Etanercept), they were followed up by regular blood liver enzymes estimations for two years. Males were thirty patients (60%), and females were twenty (40%) with a male to female ratio of 3:2 (figure-1).



**Fig-1:-** Distribution of patients according to gender.

The range of the patients age was (9-65) years with mean age of (37) years. The age range of male patients was (9-65) years and a mean age of (35.5) years, while the age range of female patients was (11-52) years and mean age of (31.5) year.

**Table-1:-** Age and gender distribution of patients.

Gender	Number	%	Age (years)	Adults (more than 14)	Children (14 and below)
Male	30	60	9-65	27	3
Female	20	40	11-52	18	2

The durations of the disease ranged from four months to forty years with a mean duration of 20.2 years. Thirteen patients (26%) had previous history of treatment with methotrexate, before they were started on Etanercept, with durations ranged from two months to twelve years (mean duration 6.1 years). Ten patients (20%) were male and the remaining three were females (6%).

Four patients (8%) had a history of previous treatment with retinoid, the durations ranged from one month to one year, all of them were males. One male patient (2%) was treated previously with both methotrexate and retinoid for three months.

The remaining 32 patients (64%) had neither treated with methotrexate nor with retinoid, of whom 20 patients (40%) were males, and 12 patients (24%) were females.

**Table-2:-** Drugs used in treatment of patients before starting Etanercept.

Type of treatment	No. of patients		Duration of other treatments	
	Male n(%)	Female n(%)	Duration	Mean
Methotrexate	10(20)	3(6)	2 months-12 years	6.1 years
Retinoid	4(8)	0(0)	1 month-1 year	6.5 month
Both	1(2)	0(0)	3 months	----
NO History	20(40)	12(24)	----	----

At baseline time of treatment all patients were presented with normal blood liver enzymes levels (AST, ALT, and ALP). During the period of follow up, two patients 4% showed increased ALT levels, another two patients 4% showed increased AST levels, one patient 2% showed increased both ALT & AST levels, and six patients 12% showed increased ALP levels. Three patients 6% showed increased levels of (ALT&/or AST) and ALP at the same time.

**Table-3:-** Patients with increased enzymes levels.

Enzyme	No. of patients	Percentage
ALT	2	4
AST	2	4
ALT & AST	1	2
ALP	6	12
(ALT&/or AST) & ALP	3	6

Table-4 showed the relationship between the increase in enzyme blood level and the type of previous treatment. Ten patients 20% had no history of previous treatments that constituted 20% of the total number of patients. Three patients had a previous history of treatment with methotrexate that constituted 6% of the total number of patients. Four patients had a history of previous treatment with retinoid that constituted 8% of the total number of patients. One patient had a history of previous treatment with methotrexate and retinoid that constituted 2% of the total number of patients.

**Table-4:-** The relationship between type of enzyme elevated and previous treatment history.

Previous treatment	Elevated enzyme				
	ALT	AST	ALT & AST	ALP	(ALT &/or AST)& ALP
	n(%)	n(%)	n(%)	n(%)	n(%)
NO history	2(4)	1(2)	1(2)	4(8)	2(4)
Methotrexate	---	1(2)	---	1(2)	1(2)
Retinoid	---	---	---	1(2)	---
Methotrexate and retinoid	---	---	---	---	---

The total number of patients with increased level of blood liver enzymes was 14 patients constituted 28% of the total number of patients studied. Four patients (8%) were children and the rest 10 patients (20%) were adults.

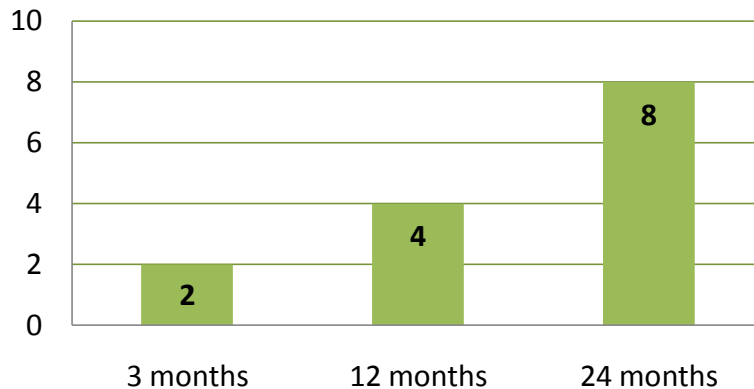
The increments in the level of blood liver enzymes were more than one fold above the upper normal limit (UNL) in 12 patients (24%), while the other two patients (4%) showed an increment of more than two fold of (UNL) the blood liver enzymes level.

Of the 12 patients with more than one UNL increment eight patients were adults and the other four patients were children, whereas those with increment of more than two UNL were one adult and one child patient.

**Table-5:-** Enzyme level status and age group of patients.

Age group of patients	Enzyme level status		
	Normal level	More than one unit	More than two units
	n(%)	n(%)	n(%)
Adults	35(70)	8(16)	1(2)
Children	1(2)	4(8)	1(2)

It was noticed that blood liver enzymes started to increase in 2 patients after 3 months of starting treatment with Etanercept, in 8 patients after 12 months, and in 4 patients after 24 months (Figure-2).



**Figure-2:-** Onset of increase in blood level of liver enzymes.

**Discussion:-**

Psoriasis is a chronic inflammatory skin disease characterized by abnormal differentiation and hyperproliferation of the epidermis <sup>(1)</sup>. The pathogenesis is incompletely understood, it is a complex multifactorial disease with a genetic predisposition <sup>(14)</sup>. The treatments of patients with severe psoriasis include systemic immunomodulatory drugs (biologics). Among these drugs are the anti-TNF inhibitors like Etanercept <sup>(12)</sup>.

Despite their many benefits, several serious side effects exist and adverse reactions do occur from the use of anti-TNF agents. One of these adverse reactions is liver injury which was observed in some patients <sup>(11)</sup>. Liver injury was assessed by liver blood tests (ALT, AST and ALP), however higher than normal levels of the liver enzymes should not be automatically equated with liver disease, as they may indicate liver problem or they may not <sup>(13)</sup>.

Patients in this study when started treatment they were with normal levels of blood liver enzymes at baseline time. During the course of treatment 14 patients showed elevations of the blood liver enzymes (ALT, AST, and ALP).

Of them the number of patients that showed elevated levels of ALT and/or AST were 5 patients (10%), those patients that showed elevated levels of ALP were six patients (12%), and those patients with elevated levels of the three liver enzymes (ALT, AST and ALP) at the same time were three patients (6%).

Van Denderon et al in their study about the frequency of liver problems associate with Etanercept treatment for ankylosing spondylitis, in which elevated serum aminotransferases was observed in 9% of cases<sup>(15)</sup>.

Regarding the increments that were observed in the blood liver enzymes, we had considered them as an elevation rather than an abnormality since the amount of increments were just one more than upper normal level in 12 patients (85.7%) of 14 patients with elevated enzymes levels, and the remaining two patients (14.3%) showed an increment of more than two the upper normal levels.

Those patients, who showed more than 2 folds increments, were a female adult and male children, both developed high levels of the enzyme ALP at sometimes during the treatment. The adult one was stopped the treatment permanently and excluded from the study, while the child patient continued the treatment since children and adolescents may have elevated levels of ALP because their bones are growing. Sokolove et al, named risk of elevated liver enzymes associated with TNF-inhibitor utilization in patients with rheumatoid arthritis, in which the overall incidence of LFT elevation of more than onefold UNL was uncommon and abnormalities of more than two fold UNL were rarely observed<sup>(16)</sup>.

The study conducted by Van Denderon et al, named the frequency of liver problems associated with treatment of ankylosing spondylitis patients with Etanercept, they defined liver disease as elevated liver enzymes of more than 1.5 times the UNL. A serious liver enzymes deviation was defined as more than 3 times UNL. This may result in permanent cessation of treatment with Etanercept<sup>(15)</sup>.

A study mentioned that any elevation of ALT above 10 times the UNL or persistent elevation above three times the UNL is appropriate criteria to stop a medication, particularly if it has been implicated in causing severe drug-induced liver injury<sup>(17)</sup>.

Regarding the time of onset of the elevations, in our study we found that blood liver enzymes levels started to increase as early as 3 months after beginning of the treatment with Etanercept in only two patients, while the other 12 patients started to show increase in liver enzymes after 12 months in 8 patients and after 24 months in 4 patients.

In the study of Leak et al about the hepatitis which can be induced by Etanercept, they found that it could occur even within one month of initiating treatment, although the usual case in which it had to take Etanercept for 12 months before hepatitis occurred<sup>(12)</sup>.

### **Conclusion:-**

It was concluded that the overall frequency of elevations in blood liver enzymes in our patients were 14 (28%) collectively, and the range was from 6-12% according to the type of the enzyme. The onset of blood liver enzyme elevations was from 3 to 24 months after starting the medication and that almost all of them showed an acceptable amount of elevations which were less than two folds of the upper normal level of the enzymes and only two patients exceeded two folds, resulted in permanently cessation of treatment in one of them.

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