INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY Vol. 23, no. 3, 965-969 (2010)

LETTER TO THE EDITOR

ETANERCEPT THERAPY IN PATIENTS WITH PSORIASIS AND CONCOMITANT HCV INFECTION

M.C. GARAVAGLIA and G. ALTOMARE

Department of Dermatology, University of Milan, Istituto Ortopedico Galeazzi IRCCS, Milan, Italy

Received February 3, 2010 – Accepted July 22, 2010

Treatment of patients with psoriasis and/or psoriatic arthritis and concomitant hepatitis C infection remains difficult. Except for cyclosporine, other drugs have proved unacceptable because of hepatotoxicity in patients with HCV. With the advent of anti-TNF-alpha drugs, including etanercept, new therapeutic options have become available. Our study population was five patients with psoriasis and/or psoriatic arthritis and concomitant chronic HCV infection undergoing etanercept therapy. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and viral load were used as markers for liver damage and disease progression, respectively. The Psoriasis Area Severity Index (PASI) was used as a reference parameter for evaluating the therapeutic efficacy of etanercept therapy in improving the clinical skin picture. AST, ALT, viral load and PASI were monitored at 3-month intervals starting from the beginning of therapy up to two years after initiation of etanercept therapy. In four out of five patients, liver enzyme levels and viral load remained substantially unchanged during the course of therapy. In the one remaining patient, viral load and liver enzyme levels increased during etanercept therapy, and then decreased following the initiation of Peg-IFN/ribavirin in combination with anti-TNF-alpha therapy. PASI scores decreased in all five patients. Our data suggest that etanercept therapy is safe and provides an efficacious therapeutic alternative in patients with psoriasis and concomitant HCV infection.

Etanercept is a fully human fusion protein consisting of the extracellular ligand-binding portion of the 75kD (p75) tumor necrosis factor (TNF) receptor linked to the Fc region of IgG1. It is synthesized by recombinant DNA technology in a Chinese hamster ovary cell line and has a longer half-life than the native soluble receptor. It is known to generally impede inflammation by binding and inactivating circulating TNF-α and β, thus competitively inhibiting the interaction between TNF and its cell surface receptors. Through this general mechanism of action, etanercept has been reported to be an effective treatment for inflammatory diseases such as psoriasis and psoriatic arthritis (PsA).

TNF, a cytokine produced primarily by mononuclear phagocytes, is a potent proinflammatory and immunoregulatory mediator and plays a central role in the pathogenesis of many inflammatory diseases. Elevated levels of TNF and its receptors have been detected in the skin of patients with psoriasis and in the joints and synovial membranes of patients with PsA (1-2).

Hepatitis C virus (HCV) infection is the most common blood-borne infectious disease, with a prevalence of approximately 1.4-1.8%. Elevated levels of TNF have been documented in patients with hepatitis C and are associated with a worse prognosis, although the exact role of TNF-α in the

Key words: etanercept, psoriasis, hepatitis C

Mailing address:
Dr Matteo Claudio Garavaglia,
Via Riccardo Galeazzi, 4
20161 Milano, Italy
Tel: ++39 02 66214958
Fax: ++39 02 66214838
e-mail: dottor77@libero.it

0394-6320 (2010)

pathogenesis of this disease is unclear(3-5).

Cyclosporine was once the only drug available for the treatment of patients with psoriasis and concomitant HCV infection (6-7) because other drugs, such as acitretin and methotrexate, are hepatotoxic in patients with HCV. Since the discovery of anti-TNF-alpha drugs, a new, effective treatment option can be offered to these patients. In this study we evaluate the effect of etanercept therapy on psoriasis, liver function and viral load in five patients with psoriasis or psoriatic arthritis and concomitant chronic HCV infection.

MATERIALS AND METHODS

The study population was five patients (1 woman, 4 men; mean age, 59 years; range, 47-72) attending the dermatology service of the Istituto Galeazzi, Milan, between 2007 and 2009, with diagnosed psoriasis and/or psoriatic arthritis and HCV infection.

Inclusion criteria:

- diagnosis of psoriasis and/or psoriatic arthritis
- positive HCV status as determined by serological testing for anti-HCV antibodies
- active etanercept therapy

All patients underwent diagnostic examination (x-ray of the spine, hands, feet, pelvis; echography of the Achilles tendon and plantar fascia) to assess: presence of concomitant psoriatic arthritis; duration of psoriasis; previous conventional drug therapy for psoriasis and hepatitis C; duration of etanercept therapy and weekly dosage (Table I). Dermatological examination was carried out using the Psoriasis Area Severity Index (PASI). The patients clinical history was also studied.

Serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and viral load were used as markers for liver function and disease progression, respectively. PASI scores were used as a reference parameter for evaluating the therapeutic efficacy of etanercept therapy in improving the clinical skin picture. ALT and AST levels were monitored by means of kinetic spectrometry; HCV viral load was measured by quantitative polymerase-chain reaction (PCR) analysis. AST, ALT, viral load and PASI were monitored at 3-month intervals from the start of treatment up to two years after the initiation of etanercept therapy.

RESULTS

In two of the five patients, a positive HCV status was discovered prior to the diagnosis of psoriasis; in the other three, infection with HCV was found after diagnosis of the disease. Two patients (Nos. 1 and 2) were also affected with psoriatic arthritis.

Liver enzyme levels were regularly monitored in all five patients. Baseline AST values in two patients (Nos.1 and 4) were higher than normal, but returned to within normal limits after etanercept therapy was initiated (Table II). Baseline ALT values in three patients (Nos. 1, 3 and 4) were higher than normal, but returned to within normal limits after etanercept therapy was initiated (Table III). Baseline AST and ALT values in one patient (No. 2) remained unchanged during the entire course of etanercept therapy. Baseline AST and ALT values in one patient (No. 5) were within the normal limits, but increased during therapy and peaked between 13 and 18 months. The subsequent decrease between 19 and 24 months was attributed to initiation of pegylated (Peg)-interferon (IFN)/ribavirin during etanercept therapy.

Viral load was measured at the start of etanercept therapy and monitored over the course of treatment in all five patients. Viral load remained substantially unchanged in three patients (Nos. 2, 3 and 4) and decreased relative to baseline values in one patient (No. 1) during etanercept therapy. Viral load increased in one patient (No. 5) during etanercept therapy, and then decreased following the initiation of Peg-IFN/ribavirin in combination with anti-TNF-alpha therapy.

PASI scores were calculated before and during etanercept therapy, and decreased in all five patients (Table IV).

DISCUSSION

Tumor necrosis factor-alpha (TNF-alpha), a cytokine that plays a central role in inflammation, is found in high concentration in the skin and joints of patients with psoriasis or psoriatic arthritis (PsA). Triggering of TNF-alpha by the macrophages and fibroblasts stimulates the production and recruitment of other inflammatory cells in the skin and joints, which are probably responsible for tissue damage. Etanercept works to inhibit cytokine function by binding to TNF-alpha receptors. Clinical studies (8-10) have shown that HCV-positive patients present with elevated levels of TNF-alpha, but its

Table I. *Patient characteristics.*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (yrs)	72	62	49	65	47
Sex	F	M	M	M	M
Duration of psoriasis since diagnosis (yrs)	14	4	19	3	32
Previous therapies for psoriasis	Cyclosporine	None*	Cyclosporine	Cyclosporine	Cyclosporine
Psoriatic arthritis	Yes	Yes	No	No	No
Duration of HCV infection since diagnosis (yrs)	15	1	2	15	17
Previous therapies for HCV	IFN	None	IFN	None	None
Duration of etanercept therapy (mths)	24	14	10	8	22
Weekly etanercept dosage	50 mg	50 mg	50 mg	50 mg	50 mg

* *conventional drug therapy contraindicated.*

Table II. *Changes in serum AST levels (range 0-35 U/L).*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Baseline	65	28	36	47	38
1-3 mths	30	28	34	45	74
4-6 mths	32	30	32	38	42
7-12 mths	35	28	36	32	52
13-18 mths	28	30			85*
19 - 24 mths	32				73

**Peg-interferon/ribavirin therapy initiated.*

Table III. *Changes in serum ALT levels (range 0-45 U/L).*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Baseline	63	35	49	54	44
1-3 mths	29	32	43	47	87
4-6 mths	27	0	45	38	81
7-12 mths	29	33	41	42	73
13-18 mths	28	28			119*
19 - 24 mths	32				75

**Peg-interferon/ribavirin therapy initiated.*

role in the progression of hepatitis remains unknown. Data suggest that TNF-alpha increases hepatocyte apoptosis and causes hepatic fibrosis in hepatic viral diseases (11-12). Hence, inhibition of TNF-alpha could control progression of the disease. Our study shows that the serum ALT and AST levels in four out of five patients remained unchanged during the course of etanercept therapy and decreased to within normal limits in one patient by the end of the study (No. 1).

Etanercept therapy was associated with an increase in liver enzyme levels and viral loads in

Table IV. *Changes in PASI scores during etanercept therapy.*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Baseline	22.5	18.3	23.8	22.4	27.3
1-3 mths	16.2	9.3	12.3	11.7	14.7
4-6 mths	7.4	0	6	4.6	12.1
7-12 mths	5.6	0	3.7	0	8.4
13-18 mths	0	0			7
19 - 24 mths	0				8.3

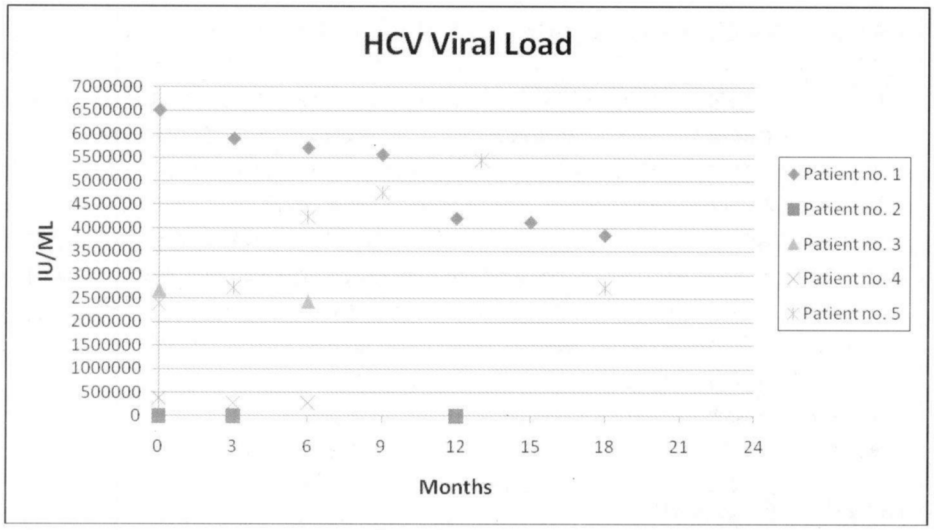

Fig. 1. *Plasma levels of HCV-RNA.*

only one patient (No. 5). After consultation with the hepatologist and in agreement with the patient, Peg-IFN/ribavirin therapy was initiated. Subsequent blood chemistry tests showed a decrease in AST and ALT levels, as well as viral load. This suggests that etanercept therapy may strengthen the effect of concurrent antiviral therapies (Peg-IFN/ribavirin). Consistent with this hypothesis are data from a double-blind study (13) which demonstrated that etanercept adjuvant to IFN/ribavirin therapy significantly improved virologic response and was associated with a lower incidence of adverse reactions of these drugs.

Our data indicate that anti-TNF-alpha drugs can be safely used in patients with psoriasis and concomitant HCV infection. Furthermore, our data are in line with those of other studies (14-16) in which serum aminotransferase levels and viral load were used as markers for liver inflammation and viral proliferation.

In conclusion, our results suggest that etanercept therapy is a safe and effective therapeutic option in patients with psoriasis and concomitant HCV infection. When used in combination with standard treatment for HCV infection, it may bring benefit.

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