

# Safety of Anti-Tumor Necrosis Factor- $\alpha$ Therapy in Patients with Rheumatoid Arthritis and Chronic Hepatitis C Virus Infection

CLODOVEO FERRI, GIANFRANCO FERRACCIOLI, DANIELA FERRARI, MAURO GALEAZZI, GIOVANNI LAPADULA, CARLOMAURIZIO MONTECUCCO, GIOVANNI TRIOLO, GABRIELE VALENTINI, and GUIDO VALESINI, for the GISEA Group

**ABSTRACT. Objective.** The prevalence of concurrent rheumatoid arthritis (RA) and hepatitis C virus (HCV) infection is probably underestimated because of the increasing spread of this virus worldwide, especially in developing countries. In these patients, anti-tumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) therapy may aggravate hepatitis and increase viremia. We evaluated the safety of these treatments, which remain controversial.

**Methods.** Thirty-one HCV-positive patients (23 women, 8 men, mean age  $59 \pm 13$  yrs, mean disease duration  $13 \pm 11.5$  SD yrs) with active RA [Disease Activity Score 28 (DAS28)  $> 3.2$ ] unresponsive to conventional therapies were treated with TNF- $\alpha$  blockers (infliximab 11, etanercept 17, adalimumab 3) at standard dosages. Safety and efficacy were evaluated at the third month of treatment and at the patient's last observation.

**Results.** A significant clinical-serological improvement was recorded at the 3-month reevaluation. Mean values of patients' assessment of general health on visual analog scale (range 0–100) decreased from  $69 \pm 29$  (SD) to  $35 \pm 27$  ( $p < 0.0001$ ), Ritchie index from  $21.6 \pm 13.9$  to  $10.1 \pm 3.7$  ( $p < 0.0001$ ), erythrocyte sedimentation rate from  $36 \pm 25$  to  $28 \pm 22$  mm/h ( $p = 0.04$ ), and DAS28 from  $5.2 \pm 1.6$  to  $2.78 \pm 1.3$  ( $p < 0.0001$ ); a DAS28  $< 2.6$  was recorded in 15/31 (48%) patients. At the last observation 19 patients (61%) continued TNF- $\alpha$  blockers, and the observed benefits persisted after  $22 \pm 11$  months of followup. Mean values of transaminases (ALT) and HCV viral load showed no significant variations; TNF- $\alpha$  blockers were discontinued in only one patient because of persistently elevated ALT not correlated to the variations of HCV viremia; this latter increased significantly ( $\geq 2 \log_{10}$ ) in 4 cases.

**Conclusion.** Previous observations had suggested the safety of TNF- $\alpha$  blockers for treatment of RA in patients with concurrent HCV infection. Given the clinical-therapeutic implications, our results support the safety of TNF- $\alpha$  blockers in patients with HCV, provided there is close monitoring of clinical and virological data (mainly ALT and HCV viremia). (First Release Aug 1 2008; J Rheumatol 2008;35:1944–9)

## Key Indexing Terms:

RHEUMATOID ARTHRITIS  
TUMOR NECROSIS FACTOR- $\alpha$  BLOCKER

HEPATITIS C VIRUS  
SAFETY

Treatments with anti-tumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) therapy are increasingly employed in patients with rheumatoid arthritis (RA) refractory to other conventional therapies<sup>1</sup>. Since TNF is a major proinflammatory cytokine that

plays an important role in the immune mediated inflammatory response to infectious agents, the anti-TNF- $\alpha$  treatments may increase susceptibility to a range of pathogens<sup>2,3</sup>. As well, they could adversely affect the out-

*From the Rheumatic Disease Unit, University of Modena and Reggio Emilia, Modena/Reggio Emilia; Rheumatic Disease Unit, Catholic University of the Sacred Heart, Rome; Rheumatic Disease Unit, University of Siena, Siena; Rheumatic Disease Unit, University of Bari, Bari; Rheumatic Disease Unit, University of Pavia, Pavia; Rheumatic Disease Unit, University of Palermo, Palermo; Rheumatic Disease Unit, University of Napoli 2, Napoli; and Rheumatic Disease Unit, Sapienza University of Rome, Rome, Italy.*

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*C. Ferri, MD, Chair of Rheumatology, Rheumatic Disease Unit, University of Modena and Reggio Emilia; G. Ferraccioli, MD, Chair of Rheumatology, Rheumatic Disease Unit, Catholic University of the Sacred Heart; D. Ferrari, MD, Fellow, Rheumatic Disease Unit, University of*

*Modena and Reggio Emilia; M. Galeazzi, MD, Chair of Rheumatology, Rheumatic Disease Unit, University of Siena; G. Lapadula, MD, Chair of Rheumatology, Rheumatic Disease Unit, University of Bari; C. Montecucco, MD, Chair of Rheumatology, Rheumatic Disease Unit, University of Pavia; G. Triolo, MD, Chair of Rheumatology, Rheumatic Disease Unit, University of Palermo; G. Valentini, MD, Chair of Rheumatology, Rheumatic Disease Unit, University of Napoli 2; G. Valesini, MD, Chair of Rheumatology, Rheumatic Disease Unit, Sapienza University of Roma.*

*Address reprint requests to Prof. C. Ferri, Cattedra di Reumatologia, Policlinico, Via del Pozzo, 71, 41100 Modena, Italy.  
E-mail: clferri@unimo.it*

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come of common viral infections such as hepatitis C virus (HCV) and the related chronic hepatitis. HCV infection represents one of the most frequent conditions in the general population worldwide, especially in areas such as Southern Europe, where its prevalence may rise to over 3%<sup>4</sup>. Considering the prevalence of RA (around 0.5%), the estimated prevalence of both disorders occurring simultaneously in an Italian population should be around 0.015%.

It can be hypothesized that inhibition of TNF by anti-TNF- $\alpha$  treatment in patients with RA with concomitant chronic HCV infection may have a number of adverse effects, from abnormally increased viral replication to an altered inflammatory process, which may significantly change the clinical course of both diseases.

A few related clinical studies, often limited to small numbers of patients, are available<sup>5-11</sup>; we report the results of a multicenter cohort study on the clinical effects and safety of anti-TNF- $\alpha$  treatments in patients with concurrent RA and HCV infection.

## MATERIALS AND METHODS

Thirty-one patients with RA and HCV infection (23 women, 8 men, mean age  $59.4 \pm 13.3$  yrs) treated with TNF- $\alpha$  blockers were included in the study (Table 1). Clinical records of these consecutive patients were collected from databases at 7 university based rheumatology units; in all cases a clinical-virological reevaluation was done at the time of our study. The disease was classified according to the American College of Rheumatology (ACR) criteria for RA<sup>12</sup>. Symmetrical, erosive polyarthritis was present in the majority of cases (27/31), while only 4 patients showed rheumatoid oligoarthritis ( $\leq 5$  joints with synovitis); moreover, rheumatoid factor (RF) and/or antibodies to cyclic citrullinated peptides (anti-CCP) were observed in 87% of cases (27/31). In particular, high titers of anti-CCP were found in 3 of 4 patients with oligoarthritis (4-5 involved joints; Table 1).

Diagnosis of chronic HCV infection was done on the basis of serum anti-HCV antibodies (commercial ELISA kits) and quantitative evaluation of HCV viremia by polymerase chain reaction (PCR) technique. In all cases the presence/absence of liver involvement was evaluated on the basis of persistent ( $\geq 6$  mo), abnormally high serum levels of alanine aminotransferase (ALT, normal values 2–40 U/l), ultrasound examination, and/or histological alterations on liver biopsy. Patients with clinical and/or histological evidence of cirrhosis were excluded from anti-TNF- $\alpha$  treatment.

Clinical and laboratory investigations excluded other relevant comorbidities, mainly cardiovascular, renal, thyroid, and/or pulmonary disorders. The presence of tuberculosis was ruled out by careful clinical and chest radiographic evaluation and tuberculin testing. The presence of various extraarticular manifestations potentially associated to RA and/or HCV infection was systematically investigated, namely, sicca syndrome, Raynaud's phenomenon, peripheral neuropathy, glomerulonephritis, interstitial lung involvement, and cryoglobulinemic vasculitis classified according to current criteria<sup>13</sup>. Moreover, circulating cryoglobulins and organ- and non-organ-specific autoantibodies, namely antithyroid, antinuclear, antiextractable nuclear antigen, anticardiolipin, anti-smooth muscle, and antimitochondrial autoantibodies were investigated by standard techniques as reported<sup>13</sup>.

The criterion to receive TNF- $\alpha$  blockers was presence of active RA with a Disease Activity Score (DAS28)  $> 3.2$  despite treatment with previous conventional therapy<sup>14</sup>; all patients were not eligible for methotrexate or leflunomide.

In all cases, the main clinical and laboratory measures were evaluated at baseline, after the first 3 months of anti-TNF- $\alpha$  treatment, and at the last visit (April-June 2007) or at the time of discontinuation of treatment.

Clinical evaluation included pain, swollen and tender joint counts, patient's assessment of general health using a visual analog scale (VAS, range 0–100), Ritchie index, and DAS28. Laboratory measures comprised erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and all the safety hematologic and biochemical measures (particularly albumin, prothrombin time, and liver enzymes, i.e. aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase). The observed variations of HCV viral load, measured by PCR technique (commercial methods) at different laboratories, were considered significant when at least  $\pm 2$  log<sub>10</sub> of baseline value; ALT variations  $> 50\%$  from baseline values were also considered significant. Finally, in all cases the presence of continuing or occult hepatitis B virus infection was excluded before anti-TNF- $\alpha$  therapy.

*Statistical analysis.* Continuous variables were expressed as the mean  $\pm$  1 standard deviation (SD). Group differences were tested for significance by 2-tailed Student's t-test, ANOVA test, chi-square test with Yates' correction, and Fisher's exact probability test, where appropriate. A value of  $p < 0.05$  was considered statistically significant.

## RESULTS

The main clinical and laboratory findings of 31 HCV-positive patients with RA treated with TNF- $\alpha$  blockers are summarized in Table 1. At the beginning of therapy, the mean duration of RA was  $13 \pm 11.5$  SD years. HCV infection preceded the onset of RA in only 8 subjects; it had been diagnosed medially  $6.3 \pm 5$  SD years before anti-TNF- $\alpha$  treatments. Liver involvement, often characterized by mild elevation of ALT with ultrasound and/or histological alterations, was documented in 17/31 (55%) patients. Liver biopsy was performed in only 3 patients with persistent ALT elevation and ultrasound alterations (Patients 3, 13, 20); all cases showed chronic active hepatitis without cirrhosis. TNF- $\alpha$  antagonists were administered at the standard dosages for 7–44 months (mean  $20 \pm 11$  SD); etanercept was used more frequently (17 patients), compared to infliximab (11 patients) and adalimumab (3 patients). All patients continued to take their previous treatments, generally low doses of steroids ( $\leq 8$  mg of 6-methylprednisolone) and/or nonsteroidal antiinflammatory drugs; only one patient (Patient 19), diagnosed for HCV infection 1 year after starting etanercept, underwent combined therapy with TNF- $\alpha$  blockers and methotrexate. In no case was antiviral treatment with interferon and/or ribavirin administered before and during anti-TNF- $\alpha$  therapy.

Cumulative data analysis showed a significant clinical and serological improvement of RA symptoms at the third month of treatment (Figure 1); in particular, VAS for patient's assessment of general health decreased significantly from  $69 \pm 29$  SD to  $35 \pm 27$  SD ( $p < 0.0001$ ), Ritchie index decreased from  $21.6 \pm 13.9$  SD to  $10.1 \pm 3.7$  SD ( $p < 0.0001$ ), DAS28 from  $5.2 \pm 1.6$  SD to  $2.78 \pm 1.3$  SD ( $p < 0.0001$ ), and ESR from  $36 \pm 25$  mm/h to  $28 \pm 22$  ( $p = 0.04$ ). At the same time, a value of DAS28  $< 2.6$  was recorded in 15/31 patients. In the majority of cases (25/31, 81%), the clinical-serological improvement persisted during the following period of TNF- $\alpha$  blocker treatment and was confirmed at the last recorded visit (Figure 1). Of interest, no

Table 1. Effects of anti-TNF- $\alpha$  treatments in patients with RA and HCV infection.

Pt	Age, Sex	RA Duration, yrs*	RA Criteria, n**	RF/ Anti-CCP	HCV Infection, yrs	Liver***	Anti-TNF- $\alpha$ Drug	Mo	DAS28			ALT, U/l			HCV RNA, Log <sup>10</sup> Values			Before/after anti-TNF- $\alpha$
									1	2	3	1	2	3	1	2	3	
1	61 F	21	5	+/-	12	+	IFX	30	6.5	2.52	3.8	96	50	53	ND	ND	ND	-/ANA+
2	63 F	35	5	+/+	6	+	IFX	8 <sup>#</sup>	8.42	1.68	4.29	24	17	21	5.8	5.9	5.7	-/-
3	56 M	1	4	+/+	11	+	IFX	12 <sup>#</sup>	7.63	1.2	2.52	54	72	61	6.5	5.0	5.1	-/-
4	73 F	15	6	-/-	1	+	IFX	16 <sup>#</sup>	6.54	1.13	2.55	44	43	30	5.5	5.8	5.6	-/-
5	81 F	10	5	+/-	15	+	IFX	7 <sup>#</sup>	5.4	1.23	1.44	41	53	60	5.7	5.0	7.7	-/-
6	69 F	3	5	-/-	1	+	IFX	9 <sup>#</sup>	4.6	3.6	2.87	29	83	53	5.5	5.6	4.9	-/-
7	41 M	5	5	+/nd	12	+	IFX	13 <sup>#</sup>	8.2	1.34	3.3	94	56	9	5.6	4.5	4.6	-/-
8	64 M	2	4	+/+	3	+	IFX	12	7.6	2.13	1.64	45	46	27	4.3	7.0	7.1	-/-
9	65 F	25	5	+/-	12	-	IFX	13	3.5	1.92	2.96	20	21	40	4.7	4.8	4.9	ANA+/ANA+
10	68 M	5	5	+/+	1	-	IFX	8 <sup>#</sup>	4.76	4.69	3.86	31	42	46	6.5	6.6	6.7	-/-
11	66 F	18	5	+/-	5	-	IFX	40 <sup>#</sup>	5.58	3.51	3.77	18	18	18	ND	ND	ND	ss; ANA+; ACLA+/-ss; ANA+; ACLA+
12	63F	29	6	-/-	9	-	ETA	27	4.2	3.6	2	20	14	12	ND	ND	ND	-/-
13	60 F	1	4	+/+	13	+	ETA	18	3.9	3.25	2.4	112	100	100	7.1	7.0	7.2	-/-
14	69 F	24	6	+/nd	13	-	ETA	11	4.98	2.92	2.86	11	10	11	4.2	6.6	6.8	-/-
15	74 F	3	4	+/+	1	-	ETA	13	6.91	2.77	3.38	38	16	15	6.8	5.0	5.2	-/cryoglobulinemia, purpura
16	71 F	14 <sup>†</sup>	4	+/+	13	+	ETA	33	4.2	4.2	3.5	33	34	22	7.7	6.4	6.5	-/ANA+
17	70 F	25	6	+/nd	7	-	ETA	36 <sup>#</sup>	5.78	3.19	4.84	18	18	18	7.4	7.1	6.0	ANA+/ANA+; ENA+
18	66 F	30	6	+/+	1	-	ETA	32 <sup>#</sup>	7.08	4.97	4	30	23	17	5.5	5.1	6.0	Sjögren's/Sjögren's
19	70 F	35	6	+/+	1 <sup>††</sup>	-	ETA	29	6.79	4.67	3.75	32	32	32	ND	5.6	5.8	ANA+/ANA+
20	37 F	15	5	+/+	1	+	ETA	10 <sup>#</sup>	5.1	3.3	3.1	110	48	145	6.2	4.5	4.6	ANA+; ENA+/ANA+; ENA+
21	27 F	11	5	+/-	6	+	ETA	23	3.8	3.15	2.45	47	36	32	7.3	6.2	6.2	-/-
22	39 M	12	5	+/-	1	-	ETA	8	3.47	2.24	1.89	37	25	20	7.1	7.0	7.3	-/-
23	62 F	10 <sup>†</sup>	4	+/+	6	-	ETA	29	3.6	1.89	1.96	18	14	18	5.8	4.5	4.6	-/-
24	52 F	1	5	-/-	3	-	ETA	44	3.5	0.13	2.09	23	23	22	6.3	6.2	6.5	-/-
25	61 F	1	4	+/-	4	+	ETA	9	4.1	2.88	2.09	50	49	45	6.5	6.8	6.8	-/-
26	70 F	2	5	-/+	1	+	ETA	12 <sup>#</sup>	4.9	4.22	3.8	41	67	35	6.6	6.3	6.8	ANA+/ANA+
27	58 M	2	5	+/nd	3	+	ETA	36	3.8	2.54	3.8	48	101	70	6.0	6.3	6.4	-/-
28	50 F	1 <sup>†</sup>	4	+/-	1	-	ETA	12	6.5	5.5	3.8	28	28	24	5.5	5.8	4.5	ANA+/ANA+
29	57 M	3 <sup>†</sup>	4	+/+	3	+	ADA	18	3.4	2.5	2.5	29	108	31	5.4	5.5	5.6	-/-
30	31 F	25	5	+/nd	10	-	ADA	17	3.4	2.1	1.7	21	17	15	6.2	4.2	4.5	-/-
31	51 M	30	6	+/nd	14	+	ADA	36	3.7	1.24	1.78	51	39	25	6.8	6.6	6.9	-/-

\*RA duration before anti-TNF- $\alpha$  therapy; \*\*number of classification criteria<sup>12</sup>; \*\*\*liver involvement before anti-TNF- $\alpha$  on the basis of abnormal ALT, ultrasound examination, or liver biopsy (Patients 3, 13, 20); <sup>†</sup>patients with oligoarthritis; <sup>††</sup>HVC was detected after 1 year of anti-TNF- $\alpha$  therapy; <sup>#</sup>anti-TNF- $\alpha$  therapy was discontinued (see text). 1: evaluated at the beginning of anti-TNF- $\alpha$  therapy; 2: after 3 months of treatment; 3: at last evaluation (last visit or dropout). RF: rheumatoid factor; anti-CCP: antibodies to cyclic citrullinated peptides; HCV: duration of hepatitis C virus infection before anti-TNF- $\alpha$  therapy; ALT: alanine aminotransferase, normal values 2-40 U/l; DAS28: Disease Activity Score; HCV RNA: viral load expressed as log10 of detected values; IFX: infliximab; ETA: etanercept; ss: sicca syndrome; ADA: adalimumab; ND: not detectable; nd: not done.

significant variations of liver enzymes, in particular ALT (mean values from  $41.7 \pm 26$  SD U/l to  $42 \pm 27$  SD, and  $36 \pm 29$  SD at the end of the followup; Figure 2), and other liver function tests (albumin, prothrombin time, and alkaline phosphatase) were observed. Similarly, HCV viral load remained stable or was reduced in the majority of subjects (Figure 2); only in 3 patients was a significant increase of viremia ( $\geq 2$  log10) observed, without clinical worsening of the liver involvement (Table 1, Patients 5, 8, and 14). The observed variations of HCV viremia and ALT values were not correlated with the presence/absence of associated low

doses of steroids. Before the treatment, one or more immunological alterations were observed in 8 patients, and in 3 others during the treatment (Table 1); only one patient developed mild symptoms of mixed cryoglobulinemia syndrome, namely orthostatic purpura, responsive to low doses of steroids. No significant variations of serum RF titer were observed after anti-TNF- $\alpha$  treatment. During the first months of treatment patients showed good compliance; at the last recorded visit 19 patients (61%) were still taking TNF- $\alpha$  blockers for a mean treatment period of  $22 \pm 11$  SD months, while 12 (39%) dropped out after 7-40 months of

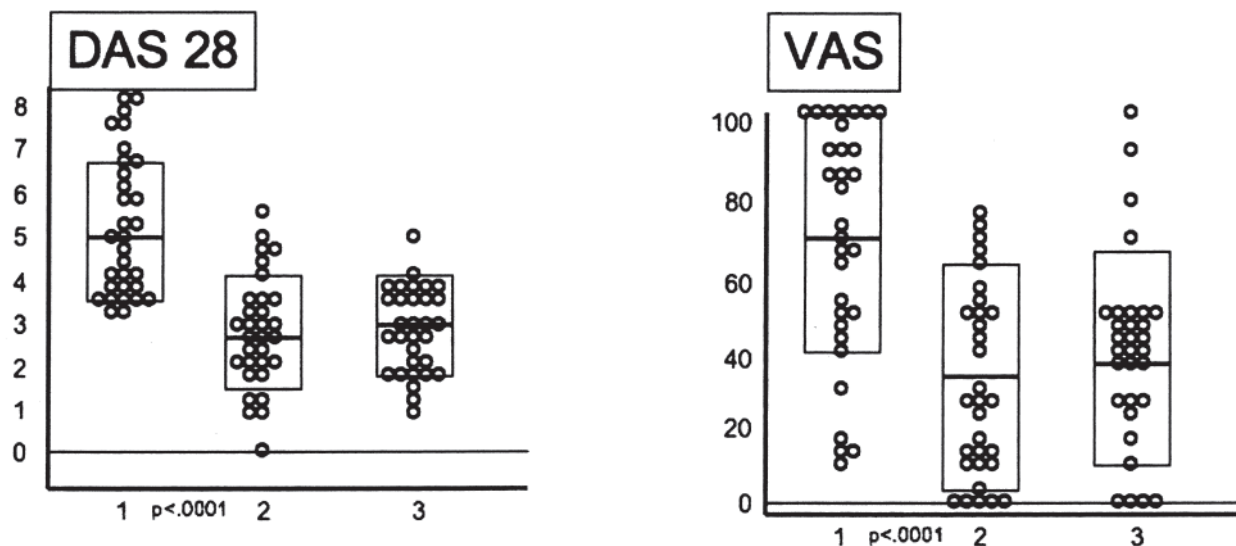


Figure 1. Clinical variations in patients with RA and HCV infection treated with anti-TNF- $\alpha$  antagonists. 1: mean values at baseline, 2: after the first 3 months of treatment, and 3: at the last recorded visit. For DAS28 the comparison between 1 and 3 showed the same statistical significance ( $p < 0.0001$ );  $p = 0.0006$  for the patients' VAS assessment of general health.

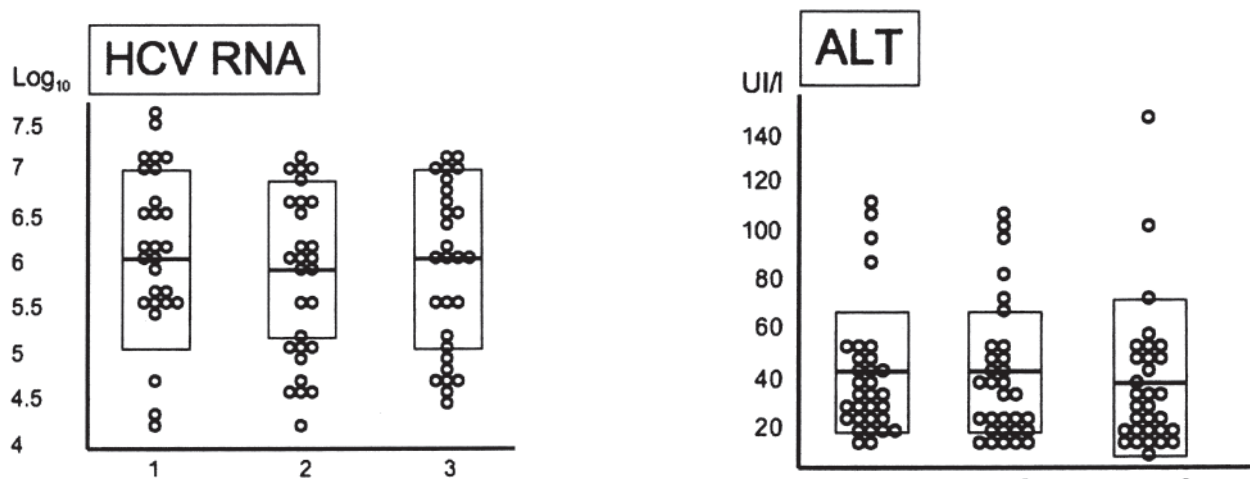


Figure 2. Mean serum levels of HCV RNA and ALT showed no statistically significant variations after the first 3 months of anti-TNF- $\alpha$  treatment (2), and at the last recorded visit (3), compared to baseline (1).

treatment (mean  $17 \pm 12$  SD) due to low compliance (2 patients; Patients 4, 5), loss of efficacy (6 patients; Patients 2, 3, 6, 7, 11, 18), persistently abnormal ALT (4 times upper limit of normal, without significant variations of viral load: 1 patient; Patient 20), colon carcinoma (1 patient; Patient 10), severe dermatitis (1 patient; Patient 17), interstitial lung involvement (1 patient; Patient 26). In no case was TNF- $\alpha$  blocker treatment complicated by opportunistic infections.

On the whole, there were not significant differences among different anti-TNF- $\alpha$  treatments in terms of safety and efficacy.

## DISCUSSION

Our study demonstrates the safety and usefulness of anti-TNF- $\alpha$  antagonists in the treatment of patients with RA and concurrent HCV infection, particularly with regard to HCV viremia and liver toxicity, as well as their efficacy in patients inadequately responsive to traditional treatments. Generally, previous therapeutic attempts were not sufficiently aggressive in individuals with HCV infection identified since the diagnosis of RA, or after the confirmation of HCV comorbidity. The first detection of HCV followed the diagnosis of RA in 2/3 patients; however, in many cases the actual

sequence of onset of the 2 diseases was difficult to ascertain. This is frequently due to the subclinical course of HCV infection, or in patients with RA diagnosed before the discovery of HCV, to the lack of available virological tests.

On the whole, the introduction of anti-TNF- $\alpha$  therapy produced a significant improvement of clinical and serological manifestations of RA. At the end of the study a relevant percentage of patients (61%) are still undergoing anti-TNF- $\alpha$  treatment, while a therapeutic failure was recorded in 1/5 cases (19%) after 8–40 months of treatment. Of interest, only one patient dropped out for possible HCV-related complications, i.e., increased transaminase levels; however, the absence of significant variations of HCV viral load argues against viral responsibility for the hepatocytolysis. Before the treatment, 8 patients had one or more serum autoantibodies or autoimmune disorders, i.e., sicca syndrome or secondary Sjogren's syndrome; during anti-TNF- $\alpha$  therapy 3 other patients showed autoantibodies — among these one developed mild mixed cryoglobulinemia syndrome. Malignancy was observed in only one patient, a 68-year-old man who developed a colon carcinoma, while opportunistic infections were never observed. The 3 TNF- $\alpha$  antagonists used were generally well tolerated, at least during the first months of treatment; however, a correct comparison between these different drugs is difficult due to the design of this retrospective study. To date, it represents the largest cohort study focusing on this specific topic; it reinforces and expands previous, often anecdotal clinical observations<sup>5–10</sup>. In terms of safety and efficacy, the results of anti-TNF- $\alpha$  therapy in this particular RA setting seem to reflect those recently observed in patients with isolated RA<sup>1,2</sup>. Only one study<sup>11</sup> has evaluated the virological and clinical effects of etanercept in a series of 24 patients with coexistence of RA and HCV infection. The authors emphasized the usefulness of anti-TNF- $\alpha$  treatment on RA activity, in the absence of significant changes of liver function tests and mean viral load<sup>11</sup>. The substantial variation of viremia in a few subjects was related to possible analytical variations in HCV RNA measurements and/or to spontaneous biological fluctuations, as demonstrated by previous virological studies<sup>11,15</sup>.

HCV is both hepatotropic and lymphotropic and potentially responsible for B-lymphocyte expansion and various organ-specific and systemic immunological disorders<sup>13,16</sup>. There is a possible pathogenetic link between chronic HCV infection and polyarthritis due to concurrent immune-complex disease; therefore, in patients with concomitant HCV infection and “arthritis” it is necessary to correctly classify their articular involvement. A mono/oligoarthritis and, less frequently, symmetrical, rheumatoid-like polyarthritis can be observed in the context of chronic HCV infection; clinically, it presents as seronegative (RF-, anti-CCP-) nonerosive arthritis with a less aggressive clinical course<sup>17–20</sup>. A careful clinical-serological investigation is recommended for a differential diagnosis between HCV-related polyarthri-

tis and classical RA with concurrent HCV infection<sup>6,21,22</sup>. This latter condition is not rare due to the prevalence of both disorders in the general population; moreover, due to the insidious clinical course of this infection, HCV screening should be mandatory, mainly in patients with “early” arthritis. Given these considerations, we carefully evaluated our patients on the basis of the ACR classification criteria for RA and the presence/absence of anti-CCP positivity<sup>12,17–22</sup>. Thus, the differential diagnosis between classical RA and HCV-related arthritis remained difficult in only a few cases.

On the other hand, the coexistence of RA and HCV infection does not represent a simple association; rather, it could be regarded as a peculiar etiopathogenetic entity: both RA and HCV infection may be responsible per se for a variety of immune-mediated complications<sup>13,16,23</sup>. During their clinical course, both articular and multiple visceral organ involvement may develop progressively; ultimately, patients with such comorbidity may display a complex overlapping syndrome that may represent a diagnostic and therapeutic challenge for the clinician. The currently used disease modifying antirheumatic drugs (DMARD), in particular methotrexate and leflunomide, may aggravate liver damage because of their potential hepatotoxicity, while corticosteroids frequently increase the HCV viral load, with unpredictable effects on hepatic and extrahepatic HCV-related complications<sup>24,25</sup>. In contrast, there is no evidence that TNF- $\alpha$  antagonists employed in RA exert direct liver toxicity<sup>26</sup>. While their potential for exacerbation of some infectious disorders, mainly tuberculosis, is well documented<sup>3</sup>, the effect of anti-TNF- $\alpha$  treatments on the clinical course of HCV infection has been investigated rarely<sup>26</sup>. Few reports underline the safety of these agents in the treatment of immune-mediated disorders and concurrent HCV infection<sup>10,26</sup>. On the other hand, Zein, *et al* evaluated the effects of etanercept as adjuvant to interferon and ribavirin in patients with chronic hepatitis C in a double-blind, placebo-controlled study; the results showed that a combined antiviral and anti-TNF- $\alpha$  treatment may significantly improve the virological response and reduce the incidence of most adverse effects associated with standard interferon/ribavirin therapy<sup>27</sup>. These interesting observations may indirectly support the known role of TNF- $\alpha$  in the pathogenesis and progression of HCV-associated liver damage; the same cytokine may be involved in the refractory response to antiviral therapy<sup>27</sup>. All these considerations including the results of our study suggest that TNF- $\alpha$  antagonists represent a safe treatment in the setting of HCV infection associated with RA. In addition, the synergic activity of combined treatment with TNF- $\alpha$  antagonists and antiviral drugs suggests new therapeutic opportunities in patients with concurrent infectious and autoimmune disorders<sup>26–28</sup>.

In conclusion, the safety of anti-TNF- $\alpha$  therapy observed in our patients is particularly relevant considering this specific subset of patients with RA: the clinical course and

prognosis of RA in chronically HCV-infected individuals are further compromised because of the potential of HCV for promoting both hepatic and extrahepatic immune-mediated disorders. Given the limitations of current DMARD, the introduction of TNF- $\alpha$  antagonists, and possibly a combined therapy with interferon and ribavirin, in patients with early RA and HCV infection should be investigated in prospective clinical trials.

## REFERENCES

1. Chen YF, Jobanputra P, Barton P, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. *Health Technol Assess* 2006;10:iii-iv, xi-xiii, 1-229.
2. Desai SB, Furst DE. Problems encountered during anti-tumor necrosis factor therapy. *Best Pract Res Clin Rheumatol* 2006;20:757-90.
3. Ellerin T, Rubin RH, Weinblatt ME. Infections and anti-tumor necrosis factor alpha therapy. *Arthritis Rheum* 2003;48:3013-22.
4. Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. *Semin Liver Dis* 2000;20:1-16.
5. Parke FA, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. *Arthritis Rheum* 2004;51:800-4.
6. Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-alpha therapy: guidelines for clinical approach. *J Gastroenterol Hepatol* 2006;21:1366-71.
7. Marotte H, Fontanges E, Bailly F, Zoulim F, Trepo C, Miossec P. Etanercept treatment for three months is safe in patients with rheumatological manifestations associated with hepatitis C virus. *Rheumatology Oxford* 2007;46:97-9.
8. Oniankitan O, Duvoux C, Challine D, et al. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. *J Rheumatol* 2004;31:107-9.
9. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. *Rheumatology Oxford* 2006;45:1294-7.
10. Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumor necrosis factor (anti-TNF) therapy in patients with chronic viral infections: hepatitis C, hepatitis B, and HIV infection. *Ann Rheum Dis* 2004;63 Suppl 2:ii18-ii24.
11. Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumor necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. *Ann Rheum Dis* 2003;62:1078-82.
12. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
13. Ferri C, Mascia MT. Cryoglobulinemic vasculitis. *Curr Opin Rheumatol* 2006;18:54-63.
14. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor- $\alpha$  blockers: The GISEA Study. *J Rheumatol* 2007;34:1670-3.
15. Arase Y, Ikeda K, Chayama K, et al. Fluctuation patterns of HCV-RNA serum level in patients with chronic hepatitis C. *J Gastroenterol* 2000;35:221-5.
16. Ferri C, Antonelli A, Mascia MT, et al. HCV-related autoimmune and neoplastic disorders: the HCV syndrome. *Dig Liver Dis* 2007;Suppl:S59-S67.
17. Buskila D. Hepatitis C associated arthritis. *Curr Opin Rheumatol* 2000;12:295-9.
18. Fadda P, La Civita L, Zignego AL, Ferri C. Hepatitis C virus infection and arthritis. A clinico-serological investigation of arthritis in patients with or without cryoglobulinemic syndrome. *Reumatismo* 2002;54:316-23.
19. Rosner I, Rozenbaum M. The case for hepatitis C arthritis. *Semin Arthritis Rheum* 2004;33:375-87.
20. Sanzone AM, Bégué RE. Hepatitis C and arthritis: an update. *Infect Dis Clin North Am* 2006;20:877-89, vii.
21. Bombardieri M, Alessandri C, Labbadia G, et al. Role of anti-cyclic citrullinated peptide antibodies in discriminating patients with rheumatoid arthritis from patients with chronic hepatitis C infection-associated polyarticular involvement. *Arthritis Res Ther* 2004;6:R137-41.
22. Palazzi C, Olivieri I, Cacciatore P, Pennese E, D'Amico E. Management of hepatitis C virus-related arthritis. *Exp Opin Pharmacother* 2005;6:27-34.
23. Khurana R, Berney SM. Clinical aspects of rheumatoid arthritis. *Pathophysiology* 2005;12:153-65.
24. Aletaha D, Kapral T, Smolen JS. Toxicity profiles of traditional disease modifying antirheumatic drugs for rheumatoid arthritis. *Ann Rheum Dis* 2003;62:482-6.
25. Choy EH, Smith C, Doré CJ, Scott DL. A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal. *Rheumatology Oxford* 2005;44:1414-21.
26. Calabrese LH, Zein N. Biologic agents and liver toxicity: an added concern or therapeutic opportunity? *Nat Clin Pract Rheumatol* 2007;3:422-3.
27. Zein NN. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol* 2005;42:315-22.
28. Niewold TB, Gibofsky A. Concomitant interferon-alpha therapy and tumor necrosis factor alpha inhibition for rheumatoid arthritis and hepatitis C. *Arthritis Rheum* 2006;54:2335-7.