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SHORT REPORT

Adalimumab is a safe option for psoriasis patients with concomitant hepatitis B or C infection: a multicentre cohort study of 37 patients and review of the literature

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Abstract

Background Little data are available about the safety of TNF-α inhibitors in patients with HCV and HBV infection. In particular, data concerning the use of adalimumab in patients with psoriasis and concomitant viral hepatitis are lacking and little is known about the drug's real safety in this context.

Objective To assess the long-term safety of adalimumab in a group of 17 consecutive psoriatic patients affected by chronic HBV infection and 20 consecutive psoriatic patients affected by chronic HCV infection.

Methods Thirty-seven consecutive patients with psoriasis and concomitant HBV or HCV infection being treated with adalimumab at four Italian referral centres (Modena, Padova, Verona and Turin) were assessed before the treatment and at the end of follow-up. Viral load and radiological studies (echography, Fibroscan) were also carried out in some of the patients.

Results The patients responded well to treatment and did not show any HBV or HCV reactivation in a mean follow-up period of 27 and 40 months, respectively. The fibrosis score in eight HCV patients showed a slight reduction: pretreatment mean value 5.83 and post-treatment mean value 5.65.

Conclusion The use of adalimumab seems to be safe in patients with severe psoriasis and HBV or HCV infection. Nevertheless, large-scale prospective studies will be able to provide vital information on the impact of anti-TNF treatment on hepatic function in patients with psoriasis and concomitant chronic HCV or HBV infection and appropriate monitoring scheduling.

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Conflicts of interest

None declared.

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Introduction

As patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection cannot participate in controlled clinical trials of anti-TNF-α, the little data that are available about their safety in patients with psoriasis have been produced by case reports and small retrospective cohort studies.

At present, etanercept is probably the most frequently prescribed biological agent in patients with psoriasis and concomitant chronic HCV or HBV infection.[1,2]

As data concerning the use of adalimumab in patients with psoriasis and concomitant viral hepatitis is lacking, little is known about the drug's real safety in this context.

The aim of this retrospective multicenter cohort study was to assess the long-term safety of adalimumab in a group of 17 consecutive psoriatic patients affected by chronic HBV infection and 20 consecutive psoriatic patients affected by chronic HCV infection.

Patients and methods

Consecutive adult patients with psoriasis and concomitant HBV or HCV infection being treated with adalimumab at four Italian referral centres (Modena, Padova, Turin and Verona) were recruited for this retrospective cohort study.

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Chronic HBV and HCV infection was defined by seropositivity of HBsAg and anti-HCV antibody for >6 months, respectively, with positive viral load.

HBV reactivation was defined as fulfilling one of the following three criteria: the development of hepatitis in association with a rise in serum HBV-DNA level to >1 log10 copies/mL higher than baseline; an absolute increase in HBV-DNA level exceeding 6 log10 copies/mL; and conversion of serum HBV-DNA test from negative to positive. HCV reactivation was defined as an increase in HCV viral load of >1 log10 IU/mL associated with a threefold increase in cytolytic activity.

All participants gave informed consent.

Data concerning chronic hepatitis were recorded 2 weeks prior to anti-TNF-α therapy, every 2–4 months during the treatment and 1–3 months post-anti-TNF-α therapy. Viral load and radiological studies (echography, Fibroscan) were carried out in some of the patients.

Results

Hepatitis B virus infection

Seventeen patients with psoriasis and HBV infection were recruited (Tables 1 and 2). The mean duration of adalimumab treatment was 27 months (3–72 months).

Ten of the 17 patients were HBsAg-positive: four of them were inactive carriers with normal transaminases, one was positive only to HBsAg and had a negative viral load, and the other five had higher liver function tests. All the HBsAg-positive patients with positive viral load were receiving prophylactic treatment with antiviral therapy (lamivudine before and entecavir after 2013). Antiviral prophylaxis lasted at least 6 months in those cases adalimumab treatment was suspended.

All the patients were stable with respect to their baseline liver enzyme tests or HBV-DNA levels.

Liver fibrosis was slightly reduced before and after adalimumab (fibrosis score 6.7 vs 6.25) in four of the studied patients.

None of the seven HBsAg-negative patients showed HBV-DNA or increased levels of transaminases. None were receiving prophylactic therapy.

Hepatitis C virus infection

Twenty patients with concomitant psoriasis and HCV were recruited (Tables 3 and 4). The mean duration of adalimumab treatment was 40 months (12–72 months).

At baseline, 14 of the 20 patients presented a negative or low viral load (<2000 UI/mL); 11 of them showed normal liver enzyme tests both before and after adalimumab treatment. Three of the patients showed an increase in liver enzymes levels during treatment even if the viral load was negative or less than 12 before treatment.

A 1-log increase in viral load was noted in three patients; one of these had less than 2000 UI/mL HCV-RNA before treatment and two had HCV-RNA >2000 UI/mL. As none of the three patients showed an increase in cytolytic indexes, they did not fulfil the criteria for HCV reactivation. Only two of the patients were treated with antiviral therapy: one with Peg-interferon/ribavirin and the other with ribavirin. The rest of the patients

Table 1 Demographic data, the Psoriasis Area Severity Index (PASI) score at baseline and end of follow-up, the duration of HBV infection and of treatment (adalimumab, ADA) in the 17 psoriasis and HBV infection patients studied

Age (years)	Sex	Psoriasis duration (years)	PASI baseline	PASI End of follow-up	HBV duration (years)	ADA therapy duration (years)
49	M	18	19	0	14	4
51	M	31	35	4	11	2
34	M	14	20	2	5	1
44	F	10	15	2	12	1
62	M	30	18	3	14	1
57	M	15	22	6	28	3
48	F	8	12	2	22	3
69	M	16	25	4	15	2
65	F	30	29	2	18	3
25	M	8	16	2	2	1
52	M	22	21	3	18	0.2
54	M	18	22	0	6	4
66	F	35	15	2	22	1.6
61	F	14	18	0	16	2.5
36	M	20	28	2	4	6
36	F	17	33	0	6	2
54	M	14	12	0	12	0.6

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Table 2 Serum liver tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelets (PTLS), HBV tests, viral load and fibroscan results, and prophylaxis used in the 17 psoriasis and concomitant HBV infection patients studied. LAM: lamivudine

AST		ALT		PTLS		HBsAg	Anti-HBsAg	Anti-HbcAg	Anti-HbeAg	HBeAg	Viral load (copies/mL)		FIBROSCAN		Antiviral prophylaxis
Baseline	End of follow-up	Baseline	End of follow-up	Baseline	End of follow-up						Baseline	End of follow-up	Baseline	End of follow-up	
30	26	31	38	199	201	+	–	–	+	–	146.6	124	ND	ND	LAM (2006–1013); ENTECAVIR (2013-now)
28	21	42	27	357	253	+	–	+	+	–	231	109	ND	ND	LAM
39	42	77	105	223	186	+	–	–	+	–	211	23	ND	ND	LAM
24	24	7	19	348	382	+	–	+	+	–	2220	0	ND	ND	LAM
72	54	84	48	96	101	+	–	+	+	–	476	392	4.90	5	LAM
88	92	76	84	122	99	+	–	–	+	–	562	498	ND	ND	LAM
37	49	35	42	109	115	+	–	+	+	–	188	98	ND	ND	LAM
96	94	92	88	95	94	+	–-	+	+	–	342	320	5.70	5.00	LAM
66	58	58	66	108	98	+	–	+	+	–	298	297	ND	ND	LAM
27	37	19	55	323	286	+	–	+	+	–	0	0	4.20	4	–
20	27	41	36	236	259	–	+	+	–	–	0	0	ND	ND	–
35	64	28	79	386	249	–	+	+	–	–	0	0	12	11	–
14	21	10	15	374	213	–	+	+	–	–	0	0	ND	ND	–
18	16	8	8	215	238	–	+	+	–	–	0	0	ND	ND	–
26	18	21	8	378	482	–	+	+	–	–	0	0	ND	ND	–
21	16	18	9	343	197	–	+	+	–	–	0	0	ND	ND	–
20	27	28	36	299	312	–	+	+	–	–	0	0	ND	ND	–

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Table 3 Demographic data, the Psoriasis Area Severity Index (PASI) score at baseline and end of follow-up, the duration of HCV and of (adalimumab) treatment in the 20 psoriasis and HCV infection patients studied

Age (yrs)	Sex	Psoriasis duration (yrs)	PASI baseline	PASI at End follow-up	HCV Duration (yrs)	ADA therapy duration (yrs)
52	M	22	15	0	15	4
50	M	25	11	4	22	6
43	M	16	30	7	5	3
62	M	31	14	4	26	4
69	F	10	10	4	23	3
49	M	5	17	0	8	3
57	M	30	12	0	16	2
41	M	15	10	7	5	3
52	M	40	24	8	4	3
58	F	18	20	2	9	4
72	M	34	8	0	21	4
49	M	28	19	1	12	2
47	F	19	16	3	3	3
62	M	30	28	0	25	5
38	F	12	11	4	10	1.5
51	M	20	21	0	9	1.5
38	M	18	14	0	6	4
31	M	11	16	2	3	1.8
42	F	21	10	0	7	1
32	F	11	10	1	11	3

had stable liver enzymes and viral load during the course of treatment.

Data on liver fibrosis were collected for eight of the patients. The fibrosis score slightly reduced (pretreatment mean value: 5.83; post-treatment mean value 5.65).

Discussion

HBV infection

HBsAg-positive patient Several studies have suggested that risk of HBV reactivation in HBsAg-positive patients may be lower in those being treated with etanercept with respect to infliximab.[2–4]

The risk associated with adalimumab remains in any case uncertain given the low number of HBV patients described in published studies.

Overall, only 19 HBsAg carriers with psoriasis treated with anti-TNF-α have been described in the literature. All were administered antiviral prophylaxis with lamivudine and none developed reactivation of hepatitis B. Only six of 19 were receiving adalimumab.[5–11]

Our data regarding 10 consecutive psoriatic patients with chronic HBV demonstrated that adalimumab does not modify the viral load or liver enzymes levels. Nine patients were taking lamivudine and one entecavir.

TNF-α seems to be able to promote hepatic fibrosis.[3] Whether the long-term suppression of TNF-α can actually play a protective role in the progression of fibrosis remains to be ascertained. Liver fibrosis was slightly reduced before and after adalimumab (fibrosis score 6.7 vs 6.25) in four of our patients. Larger long-term prospective clinical trials will be able to answer these questions.

Recent guidelines recommend treating chronic HBV patients with anti-TNF-α and an appropriate prophylactic antiviral therapy, that should start concomitantly,[12–14] and extend to 6[13] or 12[14] months after drug cessation.

Given the high resistance to lamivudine, entecavir and tenofovir have been recommended when long-term prophylaxis is needed.[4,14]

Dermatologists should cautiously prescribe anti-TNF-α to selected patients with severe psoriasis and chronic HBV infection, and etanercept and adalimumab seem to be the safest option.

HBsAg-negative patients Intrahepatic HBV-DNA can at times be detected in HBsAg-negative patients. These patients are commonly described as having 'occult HBV infection', which is defined by the presence of the HBV genome in the liver and sometimes also the serum of HBsAg-negative patients.[12]

Rheumatologic studies have shown that HBV reactivation occurs in <2% of patients with occult HBV infection treated with anti-TNF-α,[2,15] with a slightly higher risk for anti-HBs- patients than for anti-HBc+/anti-HBs+ patients.[4]

Fewer data are available regarding psoriatic patients.[16–19]

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Table 4 Serum liver tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelets (PTLS), HBV tests, viral load and fibroscan results, and prophylaxis used in the 20 psoriasis and concomitant HCV infection patients studied. IFN, interferon

AST UI/mL		ALT UI/mL		PTLS ($\times 10^3$)		Anti-HCV	RNA Baseline (UI/mL)	RNA End of follow-up (UI/mL)	FIBROSCAN Baseline	FIBROSCAN end of follow-up	Antiviral prophylaxis
Baseline	End of follow-up	Baseline	End of follow-up	Baseline	End of follow-up						
35	64	28	79	386	249	+	1286	68 846	12	11	
74	76	87	61	321	302	+	4129	409			
53	56	47	45	267	245	+	–	–			
21	65	28	118	177	146	+	2844	2312	14.2	14	RIBAVIRIN AND IFN
17	24	23	29	210	160	+	3743	43 363			
38	72	31	76	343	331	+	<12	–	4.5	4.1	
26	33	29	44	319	353	+	3952	24 000			
24	152	29	143	167	190	+	–	–			
35	66	51	100	208	201	+	5832	5911			
21	25	11	15	242	239	+	5832	5911			RIBAVIRIN
20	21	26	18	246	258	+	–	–			
66	90	49	81	178	166	+	648	702	3.2	3.2	
36	35	18	27	240	315	+	510	562	4	4.1	
96	88	78	92	106	110	+	1002	936			
40	40	32	36	136	138	+	78	162	2.9	2.9	
68	64	74	70	107	98	+	372	298			
38	34	42	40	186	205	+	216	432	3.5	3.5	
28	22	26	20	98	102	+	122	96			
26	24	28	24	164	132	+	176	142	2.4	2.4	
28	26	22	28	119	122	+	376	211			

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Only one case of reactivation was described amongst more than 100 patients with psoriasis treated with anti-TNF-α.[17]

Overall, almost two-thirds of psoriatic patients with occult HBV infection have been treated with etanercept.

The risk associated with adalimumab is nevertheless unclear given the low number of HBV patients treated with this drug. In our cohort of 17 patients with psoriasis, no cases of HBV reactivation were reported.

Patients with resolved HBV infection should be monitored carefully every 1–3 months using ALT and HBV-DNA testing.[14]

HCV infection

Concern has been expressed about the use of anti-TNF-α in chronic HCV patients.[1]

Patients with chronic HCV infections show higher production of TNF-α, which may play a role in liver injury.[20] TNF-α inhibition might thus be beneficial in HCV.

A recent systematic review examining a total of 216 HCV patients (mostly rheumatologic) exposed to anti-TNF-α for a median time of 1.2 years found that anti-TNF-α appears to be safe in these patients.[1]

In both rheumatologic and dermatologic literature, most HCV patients have been treated with etanercept.[1,11,16,21,22]

Etanercept has even been specifically evaluated as an adjunctive treatment in patients with chronic HCV in a randomized placebo-controlled trial, showing a higher sustained virologic response compared with the placebo group.[23]

As published data regarding the safety of adalimumab in patients with psoriasis diagnosed with HCV refer to less than 10 patients,[11,16,24] more studies are clearly warranted.

In our cohort of 20 consecutive psoriatic patients affected by chronic HCV treated with adalimumab (median period of 40 months), three patients showed a log rise of viral load. As this viral load increase was not associated with concurrent hepatic cytolysis, none of these patients fulfilled the criteria of HCV reactivation.

Viral load increases are not exceptional findings, and they are frequently not associated with a rise in liver enzymes and thus with hepatitis flares.[25]

Our data demonstrated adalimumab's favourable safety profiles in patients with HCV infection.

Anti-TNF-α in patients with HCV is not contraindicated, provided that liver function tests are monitored every 3 months.

Chronic HCV is a risk factor for cirrhosis and hepatocellular carcinoma (HCC), and immunosuppression might accelerate this progression. Recently, Di Nuzzo *et al.*[26] reported two cases of HCC developing in HCV psoriatic patients with cirrhotic disease during treatment with etanercept. As long-term treatment with anti-TNF-α has not been assessed in a significant number of patients with chronic HCV, careful schedules should be proposed for patients with HCV infection treated with these agents.

Limitations of the current study include its retrospective design which did not permit us to collect all data of interest and not all of our patients underwent fibroscan evaluation. As strengths, the study has a long follow-up period and, to our knowledge, it is the largest study involving patients with psoriasis coexistent with chronic HBV or HCV who were treated with adalimumab.

Large-scale prospective studies will be able to provide vital information on the impact of anti-TNF-α on hepatic function in patients with psoriasis and chronic HCV or HBV infection and appropriate monitoring scheduling.

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