The Safety of Rituximab in Hepatitis C Virus (HCV) Positive Patients

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ABSTRACT

Background: The extrahepatic manifestations of HCV infection are usually refractory to IFN-α and ribavirin. Given that the pathophysiology is autoimmune disorders, rather than the direct cytotoxicity of HCV, various immunosuppressants have been attempted, including rituximab with favorable results. However, questions on the possible opportunistic infections and hepatitis exacerbation by rituximab remain unsolved.

Methods: We hereby report 8 HCV-positive cases treated with rituximab. Indication for the treatment were severe extrahepatic conditions associated with HCV infection in 2 cases and malignant lymphoma in 6. Sequential measurements of serum transaminases, viral load, and routine clinical examination were performed for a median follow-up of 13 months.

Results: None of the 8 patients showed clinical or liver deterioration, or opportunistic infections, although 3 of them had a significant increase in HCV-load. Rituximab was well tolerated in all cases.

Conclusions: Our results further support the safety of rituximab in HCV-positive patients, providing a promising treatment modality, when needed, for HCV-associated extrahepatic disorders.

INTRODUCTION

Hepatitis C virus (HCV) infects estimated 170 million persons worldwide.[1] Chronic HCV infection can induce extrahepatic disorders, such as porphyria cutanea tarda, mixed cryoglobulinemia (MC), and a variety of renal diseases, including glomerular involvement.[2] Their response to the standard therapy with Interferon-α (IFN-α) plus ribavirin is poor and not sustained, often requiring additional immunosuppressants.

HCV-associated extrahepatic manifestations are considered antibody-mediated autoimmune disorders triggered by HCV infection, rather than the direct cytotoxicity of HCV.[3,4] Therefore, rituximab, a chimeric monoclonal antibody against CD20, has recently been used for HCV-associated MC with favorable results.[5,6] There are contradictory reports on possible hepatitis exacerbation and opportunistic infection: pure red cell aplasia due to parvovirus B19,[7] cytomegalovirus,[8] fatal varicella-zoster infection,[9] severe acute hepatitis, and fatal fulminant hepatitis.[10,11] In contrast, other authors reported that rituximab is not associated with reduction of immunoglobulin levels or increase in opportunistic infections.[11,12]

We hereby present 8 HCV-positive patients treated with rituximab, supporting the safety of the treatment in HCV-positive patients.

PATIENTS AND METHODS

Patient Characteristics

Eight HCV-positive patients were treated with rituximab; 2 for severe HCV-associated extrahepatic manifestations and 6 for CD20-positive malignant lymphoma (ML) (Table).

Patient 1 had MC and chronic membranoproliferative glomerulonephritis (MPGN), which had been refractory to IFN-α plus ribavirin, corticosteroids, and cyclophosphamide. MPGN progressed to 20 mL/min of creatinine clearance with persistent MC as previously described.[13] Patient 2 who presented with epistaxis and purpura had liver cirrhosis, leucopenia (2,000 to 3,000 white blood cells/mm^3), and episodic thrombocytopenia (1,000 to 5,000 platelets/mm^3) due to idiopathic thrombocytopenic purpura. His high dose of maintenance prednisone required splenectomy, but 18 months later thrombocytopenia recurred. The patient never tolerated IFN-α. Thrombocytopenia became refractory to corticosteroids and intravenous immunoglobulin (IVIG).

Both patients were negative for direct and indirect Coombs' test, hepatitis-B virus, cytomegalovirus, Epstein-Barr virus and human immunodeficiency virus. Administration of rituximab was approved by the Institutional Ethical Committee and written informed consent was obtained from the patients. Since rituximab is currently not indicated for the treatment of HCV-associated conditions, an additional permission was obtained from the Ministerio Español de Sanidad y Consumo.

Six patients with ML, including previously reported 3 patients,[14] received 6 or more courses of rituximab-containing chemotherapies (Table). HCV treatments with IFN-α had been given prior to rituximab in 2 patients, while the others had received no anti-HCV treatment.

HCV viral load, determined by Amplicore tests, were monitored throughout rituximab treatments. In all the cases, sequential measurements of serum transaminases and routine clinical examination were performed for a median follow-up of 13 months.

Drug Administration

Rituximab (Mabthera, Roche, Madrid, Spain) and rituximab (Rituxan, Chugai, Tokyo, Japan) were administered to

Table. Patient's Characteristics and Clinical Outcome of Patients Infected With Hepatitis C Virus

		Patient 1	Patient 2
Age/sex		69/F	45/M
Status of ML	Histology	NA	NA
	Clinical stage	NA	NA
	Disease status	NA	NA
	Cycles of chemotherapy prior to Rituximab	NA	NA
	Chemotherapeutic regimen combined with Rituximab	NA	NA
Hepatic status	Status of liver disease	Chronic active hepatitis	Cirrhosis
	Associated conditions	Chronic MPGN, Type III MC	Refractory ITP
	Duration of hepatic disease (years)	15	12
Prior treatment for hepatitis C virus		-	-
	History of Interferon-α	Yes	No tolerated
	History of Ribavirin use	Yes	No
	Other treatments	Prednisone, Cyclophosphaide	Prednisone, IVIG
	Splenectomy	No	Yes (1997)
Cycles of Rituximab administration		4	4
Genotype of HCV		1B	1A
Quantity of HCV (IU/mL) *	Pre-Rituximab	8,250	> 5,000,000
	Post-Rituximab	3,030,000	480,000
Adverse reactions		Vasovagal reaction (1st infusion)	Fever, chills (1st infusion)
Response to Rituximab containing regimes		Mild improvement of renal function Clearance of MC	
Outcomes		Alive No further liver disfunction	Alive No further liver disfunction

		Patient 5	Patient 6
Age/sex		83/F	79/M
Status of ML	Histology	Diffuse large, B cell	Diffuse large, B cell
	Clinical stage	II	II
	Disease status	Newly diagnosed	Newly diagnosed
	Cycles of chemotherapy prior to Rituximab	0	0
	Chemotherapeutic regimen combined with Rituximab	Cyclophosphamide, doxorubicin. Vincristine, prednisolone (CHOP)	Cyclophosphamide, pirarubicin. Vincristine, prednisolone (THP-COP)
Hepatic status	Status of liver disease	Chronic active hepatitis	Chronic active hepatitis
	Associated conditions	-	-
	Duration of hepatic disease (years)	1	10
Prior treatment for hepatitis C virus			
	History of Interferon-α	No	No
	History of Ribavirin use	No	No
	Other treatments	No	No
	Splenectomy	No	No
Cycles of Rituximab administration		6	4
Genotype of HCV		-	2B
Quantity of HCV (IU/mL) *	Pre-Rituximab	4,800	210,000
	Post-Rituximab	1,300	640,000
Adverse reactions		None	None
Response to Rituximab containing regimes		Complete remission	Complete remission
Outcomes		Alive In complete remission	Alive In complete remission

Patients 1 to 5 and Patients 6 to 8, respectively. In Patients 1 and 2, the infusion was initiated at 50 mg/hr during the first hour and increased to maximal 400 mg/hr if tolerated. In Patients 3 to 8, the initial infusion rate was 25 mg/hr which was increased to maximal 200 mg/hr if tolerated. All the patients

Patient 3	Patient 4
68/M	63/F
Follicular B cell	Diffuse medium, B cell
III	IV
Newly diagnosed	Refractory
0	3
Cyclophosphamide, pirarubicin. Vincristine, prednisolone (THP-COP)	None
Chronic active hepatitis	Chronic active hepatitis
-	-
15	10
-	
No	Yes
No	No
No	No
No	No
6	6
-	-
50,000	44,000
24,000	<500
None	None
Complete remission	Progression
Alive In complete remission	Died of Lymphoma progression

Patient 7	Patient 8
50/F	45/M
Diffuse large, B cell	Diffuse large, B cell
III	II
Newly diagnosed	Newly diagnosed
0	0
Cyclophosphamide, doxorubicin. Vincristine, prednisolone (CHOP)	Cyclophosphamide, doxorubicin. Vincristine, prednisolone (CHOP)
Chronic active hepatitis	Chronic active hepatitis
-	-
6	5
No	Yes
No	No
No	No
No	Yes (2002)
4	4
2B	
1,400,000	1,400,000
2,700,000	1,400,000
None	None
Complete remission	Complete remission
Alive In complete remission	Alive In complete remission

received rituximab 375mg/m^2 weekly for at least 4 weeks and premedications with acetaminophen and diphenhydramine were given.

RESULTS

Safety

Hepatitis reactivation was not observed in any patients. No bacterial or viral infections developed after rituximab (Table).

Increase in HCV-RNA load was observed in 3 cases (Patients 1, 6, and 7). Patient 1 and 7 showed no impairment in liver function tests. Patient 6 remained asymptomatic while he had reproducible grade 3 hepatotoxicity attributable to cytotoxic chemotherapy; liver function test elevated after chemotherapy and normalized thereafter, and rituximab monotherapy did not affect the declining transaminases. Anti-HCV treatment was not indicated. In the 8 patients of this group, no signs or symptoms of hepatitis developed without concurrent anti-HCV treatments, and hepatic function remained within normal limits for a median follow-up of 13 months except for Patient 4 who died of lymphoma progression.

Transient reactions to rituximab during the first infusion in Patients 1 and 2 disappeared promptly after slowing the infusion rate and additional corticosteroid, without any sequelae. Neither side effects were reported in Patients 3 to 8, nor further adverse events in subsequent administrations in Patients 1 and 2 (Table).

Efficacy

In Patient 1 creatinine clearance increased shortly after rituximab treatment and returned to baseline levels (30 mL/min) 4 months thereafter, and MC

disappeared after the treatment . Patient 2 showed a complete response with normalization of platelet counts and remains uneventful 8 months after infusions of Rituximab.

ML patients are all alive in complete response except for the one who died of ML progression (Table).

DISCUSSION

Although IFN-α plus ribavirin or pegylated IFN-α is the treatment of choice for chronic active hepatitis C,[15] less than half of the cases are expected to have a favorable response.[1] The management of extrahepatic manifestations is challenging due to their refractoriness, drug contraindications, toxicity, and adverse effects. Corticosteroids, cyclophosphamide, rituximab, and fludarabine have been introduced to refractory cases.[5,6,16,17] Possible newer agents are in various stages of preclinical and clinical development, including antisense ribozymes, protease, helicase, polymerase, immune modulation, and immunotherapy.[18]

Rituximab is well-tolerated with minimal toxicity usually limited to infusion periods. However, possible hepatitis reactivation and fatal infection are concerned. Since B lymphocytes are thought to harbor HCV,[1] it could be argued that rituximab-induced B-cell cytotoxicity would increase HCV-load. Sansonno et al reported both responders and non-responders with HCV-related MC showed B cell depletion but only the former had a simultaneous increase in HCV-RNA levels and a decline in anti-HCV-antibody titers, without significant changes of hepatocytolytic activity or deterioration of liver function in any patients.[6] These are consistent with the concept that hepatocyte damage is secondary to immunological reactions not to the direct cytotoxic effects of HCV,[3,4] promising the favorable effects of rituximab against HCV-associated disorders. While rituximab temporarily eliminates normal B lymphocytes, it is not generally associated with increased incidence of opportunistic infections.[19] Normal B lymphocytes re-emerge within weeks to months after administration of rituximab, and antibody production continues during B-lymphocytopenia because CD20-negative plasma cells are not eliminated. However, pure red cell aplasia due to parvovirus B19,[7] cytomegalovirus,[8] and fatal varicella-zoster infection[9] have been reported following rituximab.

In our series of 8 HCV-positive patients, rituximab was well-tolerated without any sign of liver dysfunction, suggesting that rituximab can be safely used in HCV-positive patients.[5,6] Enhanced viremia after rituximab, in 3 of 8 cases, however, was observed. Concurrent administration of anti-HCV agents including IFN-α and ribavirin might be reasonable to suppress HCV replication and to obtain possibly synergistic therapeutic effects against HCV-associated extrahepatic manifestations. Further studies on the safety and efficacy of rituximab are awaited.

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