



CASE REPORT

Sustained virologic response following HCV eradication in two brothers with X-linked agammaglobulinaemia

Diarmaid D Houlihan, Eoin R Storan, John M Lee

Diarmaid D Houlihan, Eoin R Storan, John M Lee, Department of Gastroenterology, University College Hospital Galway, Newcastle Road, Galway, Ireland

Author contributions: Houlihan DD and Storan ER both researched and wrote the paper; Lee JM is the consultant physician who cares for the patients; Lee JM supervised the writing of the manuscript.

Correspondence to: Dr. Diarmaid Houlihan, Department of Gastroenterology, University College Hospital Galway, Newcastle Road, Galway,

Ireland. diarmaidhoulihan@hotmail.com

Telephone: +353-87-6891649 Fax: +353-91-542289

Received: April 21, 2009 Revised: June 30, 2009

Accepted: July 7, 2009

Published online: August 21, 2009

Abstract

X-linked agammaglobulinaemia (XLA) is a humoral immunodeficiency syndrome characterized from childhood by the absence of circulating B lymphocytes, absent or reduced levels of serum immunoglobulin and recurrent bacterial infections. For many affected patients, regular treatment with immunoglobulin is life saving. Hepatitis C viral (HCV) infection acquired through contaminated blood products is widely described in this patient cohort. The natural history of HCV infection in patients with XLA tends to follow a more rapid and aggressive course compared to immunocompetent individuals. Furthermore, standard anti-viral therapy appears to be less efficacious in this patient cohort. Here we report the cases of two brothers with XLA who contracted HCV through contaminated blood products. They were treated with a six month course of Interferon alpha-2b and Ribavirin. We report a sustained virologic response five years after completing treatment.

© 2009 The WJG Press and Baishideng. All rights reserved.

Key words: Hepatitis C virus; X-linked agammaglobulinaemia; Immunodeficiency; Viral hepatitis; Cirrhosis; Hepatocellular carcinoma

Peer reviewers: Domenico Sansonno, Professor, Department of Internal Medicine and Clinical Oncology, University of Bari Medical School, Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy; Dr. Yoshiaki Iwasaki, Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1, Shikata-cho, Okayama 700-8558, Japan

Houlihan DD, Storan ER, Lee JM. Sustained virologic response following HCV eradication in two brothers with X-linked agammaglobulinaemia. *World J Gastroenterol* 2009; 15(31): 3944-3946 Available from: URL: <http://www.wjgnet.com/1007-9327/15/3944.asp> DOI: <http://dx.doi.org/10.3748/wjg.15.3944>

INTRODUCTION

Infection with the hepatitis C virus (HCV) is characterized by low grade hepatitis which may progress to cirrhosis and hepatocellular carcinoma over many years. The mortality associated with HCV infection is adversely affected by several factors including: the age of the patient at initial infection, ongoing alcohol consumption, intra-venous drug abuse and the viral genotype^[1,2]. Furthermore, the natural history of HCV infection in immunocompromised patients appears to follow a more aggressive course leading to rapid development of cirrhosis and hepatocellular carcinoma.

X-linked agammaglobulinaemia (XLA) is an inherited immunodeficiency disease caused by mutations in the gene coding for Bruton's tyrosine kinase (BTK) and occurs with a frequency of 1 in 250 000 males^[3]. Abnormal gene expression prevents B lymphocyte differentiation and maturation in the bone marrow leading to absence of circulating antibody-producing plasma cells^[4]. Furthermore, abnormalities in T cell function have been demonstrated in patients with XLA^[5]. The diagnosis of XLA may be made clinically when the following criteria are met: recurrent bacterial infections in a male infant, absence of circulating peripheral B cells and more than one male in the family affected in different generations.

Early reports of HCV infection in hypogammaglobulinaemic patients suggest a severe and rapidly progressive course^[6-9]. Initial attempts at treatment with interferon alpha demonstrated poor efficacy in maintaining virologic response and made little impact on the mortality and morbidity of those with a rapidly progressive course. Here we report the cases (diagnosis, management and follow-up) of two brothers with XLA who acquired HCV infection through infected blood products.

CASE REPORT

C.D. and J.D. are brother's aged 27 and 30 years,

respectively. They both suffered from recurrent lower respiratory tract infections as infants. Their younger brother died of pseudomonal meningitis and septicaemia as an infant. Their clinical history raised suspicion for an underlying immunodeficiency syndrome, which was confirmed when both brothers were found to be deficient in serum B cells and immunoglobulin in early childhood. Genotyping for BTK mutation was carried out and a diagnosis of XLA was established in each case. Subsequently, their cousin, who had a similar clinical history, was also diagnosed with XLA.

Both brothers were commenced on gammaglobulin infusions in 1985. This was comprised of fresh frozen plasma pooled from donors, which was not initially screened for viral contaminants. In 2002, routine biochemical analysis revealed raised liver function tests in J.D. and a full liver screen was carried out. Initial screening tests for anti-HCV including Ortho HCV ELISA Test System and Recombinant Immunoblot Assay-3 were negative. Subsequently, PCR for HCV RNA was carried out and was positive for HCV genotype 3 infection. C.D. was then screened and also found to be HCV antibody negative, but PCR positive for genotype 3 infection. The baseline viral loads were 1 723 102 copies/mL and 52 352 copies/mL for J.D. and C.D., respectively. Neither brother had risk factors for HCV infection other than their previous treatment with intravenous gammaglobulin. The results of a full infectious, metabolic and auto-immune liver screen were otherwise negative in both patients. The baseline clinical data for each patient is summarized in Table 1.

Both patients underwent a liver biopsy, which showed chronic active hepatitis. J.D. had stage 1 fibrosis with mild to moderate inflammatory activity, while C.D. had stage 0 fibrosis with mild inflammation. Both brothers were treated with a 24-wk of Pegylated Interferon alpha-2b and Ribavirin which they completed in June, 2003. There were no significant complications during treatment. Both patients were treated with antibiotics for respiratory tract infections during treatment, but did not require admission to hospital. Their viral load became undetectable 4 wk into therapy and both patients remain PCR negative five years post treatment. J.D. currently receives 35 g of Flebogamma and C.D. receives 40 g, every 3 wk, which is well tolerated by both.

DISCUSSION

Immunoglobulin therapy is widely used for the treatment of immune deficiency syndromes. Unfortunately, several outbreaks of HCV infection secondary to immunoglobulin replacement therapy have been documented in recent times. Although the true prevalence of HCV infection is difficult to estimate in this population, large studies estimate the incidence at approximately 8.3%, a number far greater than that in the immunocompetent population^[10]. Unfortunately, the diagnosis of HCV in this high risk population remains problematic for several reasons. Firstly, the poor sensitivity of traditionally used screening tests including measurement of serum

Table 1 Baseline clinical data for both patients

	Age at diagnosis (yr)	Baseline viral load	Baseline ALT (IU/L)	Liver histology	Treatment	Time to PCR negative (wk)
C.D.	27	52352 copies/mL	37 (< 42)	Mild inflammation	Peg-Interferon alpha-2b + Ribavirin	< 4
J.D.	30	1723102 copies/mL	87 (< 42)	Stage 1 fibrosis + moderate inflammation	Peg-Interferon alpha-2b + Ribavirin	< 4

aminotransferase and detection of anti-HCV antibody means that a diagnosis of HCV infection will be missed unless PCR for viral RNA is carried out. Secondly, as there is no set of international guidelines or recommendations for screening this patient cohort, there is wide variation in the screening tests employed between different centers. Finally, despite significant developments regarding viral safety for immunoglobulin preparations, clear product documentation is often absent, making early detection of HCV infection and identification and tracing of exposed individuals difficult.

The clinical course of HCV infection in patients with hypogammaglobulinaemia is unclear. Some reports suggest a rapidly progressive course with poor patient outcomes^[8,11], while others demonstrate the more usual, slowly progressive course, at least in the short term^[12,13]. A less aggressive clinical course has been observed in patients with XLA compared with those with combined variable immunodeficiency^[14], although this remains a source of debate^[15]. The variability between different trials remains unexplained. The duration of infection remains as an important predictor of patient outcome. Undoubtedly other co-morbidities including alcohol consumption, intra-venous drug abuse and co-infection with hepatitis B (HBV) adversely impact on the clinical course also. It is noteworthy that Italian patients appear to follow a more benign course following HCV infection than other populations^[13,16], suggesting a role of HCV viral load and genotype in the genesis of liver disease.

Early attempts to treat HCV infection with interferon- α monotherapy in patients with primary immunodeficiency have been disappointing^[6,8]. However, more recent data demonstrates sustained virologic responses (SVRs) of 54%^[13], and between 35%-40% approximately^[14,15], in similar patients with acute and chronic HCV infection respectively. Due to the small number of patients involved, it is difficult to determine the influence of viral load and viral genotype on treatment response. Improved treatment outcomes are seen however in patients with a shorter duration of infection and when combination therapy (Interferon and Ribavirin) is used. The excellent treatment response seen in our patients may relate to multiple factors including a favourable genotype, the young age of each patient, minimal liver fibrosis and the absence of other co-morbidities. The duration of infection is unknown as the infected batch was never identified. Although patients are considered to have achieved SVR when they remain PCR

negative six months post completion of treatment, we delayed the reporting of our patients in case of late relapse.

In conclusion, our report raises a few important points. Firstly, all patients who received intravenous immunoglobulin during periods when routine screening was not carried out, should be tested for HCV infection. The importance of measuring HCV RNA rather than looking for HCV antibodies in this patient cohort can not be overstated. Indeed, serological tests failed to make a diagnosis of active HCV infection in both our patients. Secondly, the successful outcome of treatment in both patients highlights the limited role of humoral immunity in the mechanisms of HCV clearance. Finally, despite pessimistic initial reports, the diagnosis and treatment of HCV infection in patients with XLA can lead to excellent long-term outcomes.

REFERENCES

- 1 **Niederer C**, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, Nawrocki M, Kruska L, Hensel F, Petry W, Haussinger D. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. *Hepatology* 1998; **28**: 1687-1695
- 2 **Bellentani S**, Pozzato G, Saccoccio G, Crovatto M, Croce LS, Mazzoran L, Masutti F, Cristianini G, Tiribelli C. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. *Gut* 1999; **44**: 874-880
- 3 **Kumar A**, Teuber SS, Gershwin ME. Current perspectives on primary immunodeficiency diseases. *Clin Dev Immunol* 2006; **13**: 223-259
- 4 **Conley ME**. B cells in patients with X-linked agammaglobulinemia. *J Immunol* 1985; **134**: 3070-3074
- 5 **Rozyńska KE**, Spickett GP, Millrain M, Edwards A, Bryant A, Webster AD, Farrant J. Accessory and T cell defects in acquired and inherited hypogammaglobulinaemia. *Clin Exp Immunol* 1989; **78**: 1-6
- 6 **Thomson BJ**, Doran M, Lever AM, Webster AD. Alpha-interferon therapy for non-A, non-B hepatitis transmitted by gammaglobulin replacement therapy. *Lancet* 1987; **1**: 539-541
- 7 **Bjorkander J**, Cunningham-Rundles C, Lundin P, Olsson R, Soderstrom R, Hanson LA. Intravenous immunoglobulin prophylaxis causing liver damage in 16 of 77 patients with hypogammaglobulinemia or IgG subclass deficiency. *Am J Med* 1988; **84**: 107-111
- 8 **Bjoro K**, Froland SS, Yun Z, Samdal HH, Haaland T. Hepatitis C infection in patients with primary hypogammaglobulinemia after treatment with contaminated immune globulin. *N Engl J Med* 1994; **331**: 1607-1611
- 9 **Jonas MM**, Baron MJ, Bresee JS, Schneider LC. Clinical and virologic features of hepatitis C virus infection associated with intravenous immunoglobulin. *Pediatrics* 1996; **98**: 211-215
- 10 **Quinti I**, Pierdominici M, Marziali M, Giovannetti A, Donnanno S, Chapel H, Bjorkander J, Aiuti F. European surveillance of immunoglobulin safety--results of initial survey of 1243 patients with primary immunodeficiencies in 16 countries. *Clin Immunol* 2002; **104**: 231-236
- 11 **Rossi G**, Tucci A, Cariani E, Ravaggi A, Rossini A, Radaeli E. Outbreak of hepatitis C virus infection in patients with hematologic disorders treated with intravenous immunoglobulins: different prognosis according to the immune status. *Blood* 1997; **90**: 1309-1314
- 12 **Quinti I**, Pandolfi F, Paganelli R, el Salman D, Giovannetti A, Rosso R, Oliva A, Rainaldi L, Aiuti F. HCV infection in patients with primary defects of immunoglobulin production. *Clin Exp Immunol* 1995; **102**: 11-16
- 13 **Christie JM**, Healey CJ, Watson J, Wong VS, Duddridge M, Snowden N, Rosenberg WM, Fleming KA, Chapel H, Chapman RW. Clinical outcome of hypogammaglobulinaemic patients following outbreak of acute hepatitis C: 2 year follow up. *Clin Exp Immunol* 1997; **110**: 4-8
- 14 **Bjoro K**, Skaug K, Haaland T, Froland SS. Long-term outcome of chronic hepatitis C virus infection in primary hypogammaglobulinaemia. *QJM* 1999; **92**: 433-441
- 15 **Razvi S**, Schneider L, Jonas MM, Cunningham-Rundles C. Outcome of intravenous immunoglobulin-transmitted hepatitis C virus infection in primary immunodeficiency. *Clin Immunol* 2001; **101**: 284-288
- 16 **Alberti A**, Morsica G, Chemello L, Cavalletto D, Noventa F, Pontisso P, Ruol A. Hepatitis C viraemia and liver disease in symptom-free individuals with anti-HCV. *Lancet* 1992; **340**: 697-698

S- Editor Tian L L- Editor Alpini GD E- Editor Ma WH