Granulocyte colony-stimulating factor as a novel adjunct to improve hepatitis B vaccination

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Abstract

Hepatitis B vaccination is successful in 95% of individuals. In the remainder, despite repeated attempts, immunization often remains unsuccessful. 'Non-response' leaves the individual susceptible to infection. Various strategies have been employed to overcome this. These include the use of adjuncts alongside conventional vaccines which activate immune responses. In this case report we demonstrate the successful use of the hematopoietic growth factor Granulocyte colony-stimulating factor (G-CSF) as a vaccine adjunct in an individual who had previously failed conventional vaccination three times. The patient tolerated the regimen without any side effects and achieved a hepatitis B surface antibody titer greater than 100 IU/mL. Use of G-CSF as a vaccine adjunct for hepatitis B has not previously been reported and the outcome in this case suggests that the use of G-CSF in this context warrants further exploration.

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Key words: Hepatitis B; Vaccination; Adjunct; Granulocyte colony-stimulating factor

INTRODUCTION

WHO recommend universal vaccination with the hepatitis B virus envelope protein (HBsAg) as prophylaxis against hepatitis B virus (HBV) infection. Population based studies in Taiwan conclusively demonstrate that vaccination is an effective intervention to prevent chronic HBV infection and to reduce the risk of liver cancer[1]. Successful vaccination generates antibodies to HBsAg (anti-HBs) at a titer greater than 100 IU/mL which appears to confer durable protection from infection. However, 5%-10% of individuals will fail to develop protective levels of anti-HBs after a conventional course of hepatitis B vaccination[2]. Non-response, defined as a level of anti-HBs less than 10 IU/mL, is more common in people at the extremes of age, smokers, people who are obese and those with chronic conditions such as diabetes mellitus, chronic renal failure, and human immunodeficiency virus (HIV)[3,4]. There also appears to be a genetic basis for non-response and a common observation in non responders is a lower cytokine response to the vaccine[5].

Several methods have been postulated to improve vaccine outcome by improving delivery to antigen presenting cells or by inducing the production of immunomodulatory cytokines. These include increasing the dose of the vaccine and the route of vaccine delivery[2]. Several studies have looked at the use of Granulocyte macrophage colony stimulating factor (GM-CSF) as a...
hepatitis B vaccine adjunct to boost cytokine levels. A meta-analysis of seven studies looking at hepatitis B vaccination in patients with chronic renal failure has shown GM-CSF to statistically improve vaccination rates. In contrast to GM-CSF, Granulocyte colony stimulating factor (G-CSF) is regarded as a lineage specific colony stimulating factor. It mainly affects neutrophils but does also affect antigen presenting cells. This includes a stimulatory effect on Th2 lymphocyte-inducing dendritic cells. A comparative study has suggested that G-CSF is better tolerated than GM-CSF. G-CSF has been used primarily for the treatment of neutropaenia post chemotherapy and in the process of stem cell harvesting. It has not, however, thus far been used as a vaccine adjunct.

CASE REPORT

We describe the case of a 40 year old male with type 1 diabetes since adolescence. He and his partner, a patient with chronic hepatitis B infection, planned to start a family. He had previously received 2 accelerated courses of HBV vaccination with Engerix-B. Following each course no anti-HBs was detectable. A third attempt to generate a vaccine response used an accelerated course of the Twinrix, combined Hepatitis A and B, vaccine. The Twinrix vaccine was chosen as previous reports have identified improved rates of successful vaccination compared with monovalent vaccination. Despite this, an anti-HBs response was not detected. The patient was, however, successfully vaccinated against Hepatitis A.

He was overweight with a body mass index of 29.4 kg/m². He was noted to have good glycaemic control with HbA1C of 6.4. He did not have any evidence of end organ damage and in particular had an estimated creatinine clearance of 130 mL/min. In addition, he did not have any other co-morbidity and, of note, was HIV negative. A further accelerated course (three doses) of Twinrix vaccine was administered subcutaneously again at 0, 14 and 21 d. Each dose was administered at the same time as 300 µg of subcutaneous G-CSF (Neupogen). This was the only adjunct used alongside the accelerated vaccine regimen. He tolerated this vaccination regimen well and had no side effects of note.

Serum analysis was performed 2 mo after his last injection and demonstrated an anti-HBs titre of greater than 100 indicating successful vaccination.

DISCUSSION

This case suggests that G-CSF may be used as a hepatitis B vaccine adjunct in subjects who fail to respond to conventional vaccination regimens. Whilst new vaccines are currently in development promising greater immunogenicity, the increasing use of adjuncts allows for improved vaccination success with the current generation of vaccines. Other vaccine adjuvants that have been used in Hepatitis B vaccination include GM-CSF, type 1 interferons, ASO4, ASO2A and CPG 7907.

As previously stated, a number of published studies have highlighted the efficacy of GM-CSF as a vaccine adjunct at the dose of 300 µg. At this dose G-CSF is marginally more expensive than G-CSF. However G-CSF may be equally or potentially be more efficacious than GM-CSF. Previous reports have also suggested that G-CSF may be better tolerated than GM-CSF.

It is likely that the success of G-CSF as a vaccine adjunct is due to its stimulatory effect on antigen presenting cells. Its effects otherwise are in the main limited to the terminal differentiation of neutrophils with a much lesser multi-lineage effect than GM-CSF.

Further studies are needed to confirm our results and to compare G-CSF with the other commonly used vaccine adjuvants in hepatitis B.

REFERENCES

1. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, Liang DC, Shau WY, Chen DS. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 1997; 336: 1855-1859
2. Zuckerman JN. Protective efficacy, immunotherapeutic potential, and safety of hepatitis B vaccines. J Med Virol 2006; 78: 169-177
3. Buter KP, Diepersloot RJ, Wimans PF, Gmelig Meyling FH, Hoekstra JB, Heijtink RA, van Hattum J. Humoral immune response to a yeast-derived hepatitis B vaccine in patients with type 1 diabetes mellitus. Diabet Med 1992; 9: 66-69
4. Li VS, Caruso-Nicoletti M, Biazzo F, Sciaccia A, Mandara G, Mancuso M. Hyporesponsiveness to intradermal administration of hepatitis B vaccine in insulin dependent diabetes mellitus. Arch Dis Child 1998; 78: 54-57
5. Fisman DN, Agrawal D, Leder K. The effect of age on immunologic response to recombinant hepatitis B vaccine: a meta-analysis. Clin Infect Dis 2002; 35: 1368-1375
6. Fabrizi F, Martin P, Dixit V, Bunnapradit S, Dulai G. Meta-analysis: the effect of age on immunological response to hepatitis B vaccine in end-stage renal disease. Aliment Pharmacol Ther 2004; 20: 1053-1062
7. Yamashiki M, Kosaka Y, Kondo I, Nomoto M. Impaired cytokine production by peripheral T lymphocytes in low responders to hepatitis B vaccination. Clin Sci (Lond) 1997; 92: 527-528
8. Höhler T, Reuss E, Evers N, Dietrich E, Rittner C, Freitag CM, Vollmar J, Schneider PM, Fimmers R. Differential genetic determination of immune responsiveness to hepatitis B surface antigen and to hepatitis A virus: a vaccination study in twins. Lancet 2002; 360: 991-995
9. Fabrizi F, Ganesan SV, Dixit V, Martin P. Meta-analysis: the adjuvant role of granulocyte macrophage-colony stimulating factor on immunological response to hepatitis B virus vaccine in end-stage renal disease. Aliment Pharmacol Ther 2006; 24: 789-796
10. Arpinati M, Green CL, Heimfeld S, Heuser JE, Anasetti C. Granulocyte-colony stimulating factor mobilizes T helper 2-inducing dendritic cells. Blood 2000; 95: 2484-2490
11. Weaver CH, Schultman KA, Wilson-Riley B, Birch R, West W, Buckner CD. Randomized trial of filgrastim, sargramostim, or sequential sargramostim and filgrastim after myelosuppressive chemotherapy for the harvesting of peripheral-blood stem cells. J Clin Oncol 2000; 18: 43-53
12. Nyström J, Cardell K, Björnsdottir TB, Fryden A, Hultgren C, Sällberg M. Improved cell mediated immune responses after
successful re-vaccination of non-responders to the hepatitis B virus surface antigen (HBsAg) vaccine using the combined hepatitis A and B vaccine. *Vaccine* 2008; 26: 5967-5972

13 Miquilena-Colina ME, Lozano-Rodríguez T, García-Pozo L, Sáez A, Rizza P, Capone J, Rapicetta M, Chionne P, Capobianchi M, Selleri M, Castilletti C, Belardelli F, Iacono OL, García-Monzón C. Recombinant interferon-alpha2b improves immune response to hepatitis B vaccination in haemodialysis patients: results of a randomised clinical trial. *Vaccine* 2009; 27: 5654-5660

14 Pichichero ME. Improving vaccine delivery using novel adjuvant systems. *Hum Vaccin* 2008; 4: 262-270

15 Waxman IM, Militano O, Baldinger L, Roman E, Qualter E, Morris E, Garvin J, Bradley MB, Bhatia M, Satwani P, George D, Del Toro G, Hawks R, Wolownik K, Foley S, Cheung YK, Schwartz J, van de Ven C, Baxter-Lowe LA, Cairo MS. Sequential administration of sargramostim and filgrastim in pediatric allogeneic stem cell transplantation recipients undergoing myeloablative conditioning. *Pediatr Transplant* 2009; 13: 464-474

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