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Lettere all'Editore

Letters to the Editor

Specific immunoglobulins against hepatitis C virus. Why not?

Immunoglobuline specifiche contro il virus dell'epatite C. Perché non si realizzano?

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Hepatitis C virus (HCV) infection is a major global health concern. About 200 million individuals are infected worldwide, four million in the USA alone. Hepatitis C infection often evolves to liver cirrhosis and liver cancer, and there is no vaccine against this virus. Many individuals with liver cirrhosis consequent to hepatitis C infection are candidates for liver transplant. Several dozens of thousands of patients with HCV-related liver cirrhosis are on waiting lists for liver transplantation. About 2500 liver transplants are performed every year in the USA for HCV-related liver disease, but the new liver unfailingly becomes reinfected and in many cases evolves to cirrhosis.

By contrast, in the case of hepatitis B infection, which also evolves to liver cirrhosis, there are specific immunoglobulins against this virus that contain high concentrations of neutralizing antibodies against the virus, thereby preventing reinfection of the transplanted liver. This drug inoculated about every 2-3 months ensures that the patient can enjoy a good quality of life for many years.

At present, two methods are available for the production of polyclonal immunoglobulins against hepatitis C virus: one is based on anti-HCV-positive antibodies (the "Cummins" method), and one on HCV-neutralizing antibodies (the "Piazza method").

CUMMINS METHOD

Consequent to the discovery of HCV and of anti-HCV antibodies which are present in 2-3% of blood units, in 1991 Cummins described a method for producing immunoglobulins against hepatitis C virus using anti-HCV-positive blood units that contain a high titre (>1:100) of anti-HCV antibodies (c100-3) [1]. These anti-HCV immunoglobulins are produced according to the alcohol fractionation (Cohn) method and additional inactivation techniques (TNBP/Tween 80) [1]. The Cummins method was used to produce a human hepatitis C globulin. In a randomized controlled trial, these immunoglobulins were used in 18 liver transplant patients with hepatitis C-induced end-stage liver failure with the aim of preventing reinfection of the new liver. The drug administered was based on protein concentration (two groups of patients treated with 75 or 200 mg/kg body weight, respectively); all patients were reinfected by HCV [2]. This result may be attributable to the fact that the product was not based on neutralizing antibody levels. In reporting the results of the study, the authors stated "… prevention of reinfection of the allograft by neutralizing antibody infusions would be desirable in this setting" which is the standard of care in the management of patients transplanted for HBV infection [2].

PIAZZA METHOD

It was long believed that HCV does not elicit neutralizing antibodies. In 1993, HCV-neutralizing antibodies were discovered and methods were reported [3-6]. These antibodies are present in anti-HCV-positive blood units but not in anti-HCV-negative blood units [4]. It is important to note that the titre of anti-HCV antibodies in anti-HCV-positive blood units does not correlate with the titre of HCV-neutralizing antibodies (e.g., the same blood unit can have a high titre of anti-HCV antibodies and a low titre of

HCV-neutralizing antibodies). Experimental and clinical data indicate that these neutralizing antibodies are protective against HCV infection [5, 7-9, 10]. In fact, high titers of neutralizing antibodies significantly protected both chimpanzees challenged with HCV and humans exposed to sexual transmission of HCV infection [5, 7]. Finally, the appearance of high titres of neutralizing antibodies coincided with the disappearance of virus and clinical resolution of hepatitis in patients with chronic hepatitis C [10].
In this scenario, Piazza conceived the idea of producing anti-HCV specific immunoglobulins from HCV-positive blood units, using only those units that contain a high titre of HCV-neutralizing antibodies. At the same time (1994), it was demonstrated that hepatitis C virus mutates [11]. Therefore, a drug produced from a large number of the above-mentioned blood units contains a high concentration of neutralizing antibodies against the different HCV strains which represent the active ingredient of the drug. Acting simultaneously these neutralizing antibodies would be effective against the various HCV strains. This specific immunoglobulin against HCV is produced according to the Cohn method and new additional viral inactivation procedures. The European and USA patent offices recognized that a drug produced with this method constitutes the polyclonal specific immunoglobulin against HCV, and an advance with respect to the Cummins method, and therefore granted the patents for its production [12, 13].
It is noteworthy that:

1. These specific anti-HCV immunoglobulins are expressed in I.U. They can be used in patients because, like other specific immunoglobulins (for example, those against HBV) they are very likely free of side effects because they are based on neutralizing antibody level and not on protein concentration.
2. Specific immunoglobulins against HCV have indications in various areas (prevention of reinfection of transplanted liver; post-exposure prophylaxis to the virus, about 600,000 accidental needlestick injuries occur every year in USA), and in many other situations in which individuals are exposed to the risk of acquiring HCV infection, e.g. partners of HCV-infected patients, patients undergoing haemodialysis, dental therapy or chiropody, drug abusers and lastly, in particular cases, in the treatment of chronic hepatitis C together with other drugs, etc.
3. The chance of using the chimera mouse, which is universally considered the best animal model for HCV infection instead of the chimpanzee, expedites the preclinical development of the drug. In fact polyclonal immunoglobulin, containing a high concentration of neutralizing antibodies, prepared from a patient with chronic hepatitis C, protected most chimeric mice from infection with a homologous HCV strain, while it was less effective if different genotypes were used [14, 15].
4. There is no longer concern about using anti-HCV-positive blood units as starting material due to the availability of inactivation methods that ensure the safety of the final product as regards HCV and all existing infective agents [2, 16].

CONCLUSION

Specific immonoglobulins against HCV, produced with the Piazza method contain a high concentration of neutralizing antibodies against the different HCV strains, which represent the active ingredient of the drug. These neutralizing antibodies against the different HCV strains, acting simultaneously, can block HCV infection.
Given the above, it would appear that such a drug would be easy to produce, safe, widely applicable, have the potential to save many lives and allow the administration of the high titres of neutralizing antibodies necessary to block, for example, reinfection of a transplanted liver.
It is inexplicable that such a drug, which has a very high chance of success and could save many lives, has not yet been produced!

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