replaced by parenteral drug addiction or sexual transmission.[4,5] It is not surprising that prevention is the most adequate and cost-effective control measure for these patients.

Treating chronic HCV before kidney transplantation is currently not an essential criteria for including HCV-positive patients on the transplant waiting list. However, risk of post-transplant chronic hepatitis C and the difficulty to treat it at this stage of the chronic kidney disease have been reported.[6-11]

Pegylated interferon and interferon + ribavirin are better than conventional interferon, according to clinical trials. However, the differences are small. Combining ribavirin and pegylated interferon requires close follow-up during haemodialysis given the severity of the secondary effects. It has increased the sustained viral response, although it is still less in the population without chronic kidney disease.[12] This, along with the difficulty of treating patients with stages 4 and 5 chronic kidney disease in predialysis, highlights the importance of resolving the infection at early kidney disease stages.

Transjugular liver biopsy reduces the risks of bleeding associated with this procedure and the kidney patient, although there is little evidence in the literature.[13,14] This technique also allows the hepatic venous pressure gradient to be measured, providing diagnostic and prognostic data.

Studies that determine whether the association of protease inhibitors (telaprevir, boceprevir) with interferon and ribavirin is safe for kidney patients and may increase viral response rates.

1. Aoufi Rabih S, García Agudo R. Manejo de la infección por el VHC en la enfermedad renal crónica. Nefrologia 2011;31(3):260-7.
2. Fissell RB, Bragg-Gresaham JL, Woods JD, Jadoul M, Gillespie B, Hedderwick SA, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. Kidney Int 2004;65(6):2335-42.
3. Sivapalasingam S, Malak SF, Sullivan JF, Lorch J, Sepkowitz KA. High prevalence of hepatitis C infection among patients receiving hemodialysis at an urban dialysis center. Infect Control Hosp Epidemiol 2002; 23(6):319-24.
4. Hinrichsen H, Leimenstoll G, Stegen G, Schrader H, Fölsch UR, Schmidt WE; PHV Study Group. Prevalence and risk factors of hepatitis C virus infection in haemodialysis patients: a multicentre study in 2796 patients. Gut 2002;51(3):429-33.
5. Huraib S, Al-Rashed R, Aldrees A, Aljefry M, Arif M, Al-Faleh FA. High prevalence of and risk factors for hepatitis C in haemodialysis patients in Saudi Arabia: a need for new dialysis strategies. Nephrol Dial Transplant 1995;10(4):470-4.
6. Hanafusa T, Ichikawa Y, Kishikawa H, Kyo M, Fukunishi T, Kokado Y, et al. Retrospective study on the impact of hepatitis C virus infection on kidney transplant patients over 20 years. Transplantation 1998;66(4):471-6.
7. Bruchfeld A, Wilczek H, Elinder CG. Hepatitis C infection, time in renal replacement therapy, and outcome after kidney transplantation. Transplantation 2004;78(5):745-50.
8. Gentil MA, Rocha JL, Rodríguez-Algarra G, Pereira P, López R, Bernal G, et al. Impaired kidney transplant survival in patients with antibodies to hepatitis C virus. Nephrol Dial Transplant 1999;14(10):2455-60.
9. Gheith OA, Saad MA, Hassan AA, A-Eldeeb S, Agroudy AE, Esaza H, et al. Hepatic dysfunction in kidney transplant recipients: prevalence and impact on graft and patient survival. Clin Exp Nephrol 2007;11(4):309-15.
10. Kamar N, Ribes D, Izopet J, Rostaing L. Treatment of hepatitis C virus infection (HCV) after renal transplantation: implications for HCV positive dialysis patients awaiting a kidney transplant. Transplantation 2006;82(7):853-6.
11. Toth CM, Pascual M, Chung RT, Graeme-Cook F, Dienstag JL, Bhan AK, et al. Hepatitis C virus-associated fibrosing cholestatic hepatitis after renal transplantation: response to interferon-alpha therapy. Transplantation 1998;66(9):1254-8.
12. Fabrizi F, Dixit V, Martin P, Messa P. Combined antiviral therapy of hepatitis C virus in dialysis patients: meta-analysis of clinical trials. J Viral Hepat 2010. doi: 10.1111/j.1365-2893.2010.01405.x. [Epub ahead of print]
13. De Paula Farra K, Carmo RA, De Figueiredo Antunes CM, Serufo JC, Nobre Júnior VA. Hepatitis C, HCV genotypes and hepatic siderosis in patients with chronic renal failure on haemodialysis in Brazil. Nephrol Dial Transplant 2007;22:2027-31.
14. García Agudo R, Aoufi Rabih S, Pérez Roldán F, Guzmán Ames F, González Carro P, Ruiz Carrillo F, Cuesta Domínguez R. El gradiente de presión venoso hepático y la biopsia hepática transyugular en la evaluación de los pacientes con insuficiencia renal y hepatopatía crónica. Nefrologia 2011; 31(4):490-2.

R. García Agudo[1], S. Aoufi Rabih[2]

[1] Nephrology Department. La Mancha-Centro Hospital Complex. Alcázar de San Juan, Ciudad Real, Spain.

[2] Digestive System Department. La Mancha-Centro Hospital Complex. Alcázar de San Juan, Ciudad Real, Spain.

Correspondence: R. García Agudo
Servicio de Nefrología. Complejo Hospitalario La Mancha-Centro. Enebro, 17.
13600, Alcázar de San Juan. Ciudad Real.
rgarciaagudo@hotmail.com
rganefrologia@hotmail.com

Cyclophosphamide-induced lupus flare?: the role of C4 and interferon-gamma in lupus flare

Nefrologia 2011;31(5):608-9
doi: 10.3265/Nefrologia.pre2011.Jun.10942

To the Editor,

We read with great interest the contribution by Heras, et al.[1]. They reported a significant case that seemed not to respond to intravenous (IV) cyclophosphamide (CPM) induction treatment at 1 g but to respond to increased CPM dose to 1.5 g. Reading the case report, we wondered whether CPM certainly induced the lupus flare or other mechanisms were involved in the pathogenesis. They speculated

that the lupus flare might have been due to the initial underdosing of cyclophosphamide. This explanation is plausible, but we would like to say that lupus flares can occur during or after stopping CPM treatment, suggesting the possible pathomechanisms of lupus flare.

In the immunological test after the first treatment of IV CPM, the patient had increased C3 level, but C4 was decreased. According to a previous study by Ho, et al.[2], a decrease in C4 was associated with a concurrent increase in renal disease activity ($p = 0.02$). A decrease in C4 was especially associated with concurrent decreases in the hematocrit levels ($p = 0.009$), and previous increases in C3 were also associated with a higher frequency of decrease in platelet counts ($p = 0.02$). These data show that the renal and hematologic systemic lupus erythematosus (SLE) activity and flares are strongly associated with decreased C4.

Recently, Finke, et al.[3] demonstrated that complement C4-deficient mice result in elevated intravascular levels of apoptotic DNA, targeted to the splenic marginal zone where it accumulates and induces type I interferon-gamma (IFN-γ). Type I IFN-γ is important for the initiation and potentiation of SLE activity and correlated with the renal disease and the presence of cutaneous manifestations[4].

Therefore, we suggest that CPM is not an inducer but an inhibitor of lupus flare, and decreases in C4 and increased type I IFN-γ might play the central role in the development of lupus activity and flares. However, further studies are necessary to elucidate the exact molecular roles of complement deficiency and elevated levels of IFN-γ. The potential therapeutic antibodies directed to either type I IFN-γ or IFN α chain of the receptor 1 (IFNAR1)/IFNAR2 should also be further evaluated in the future.

1. Heras M, Saiz A, Fernández-Reyes MJ, Sánchez R, Zurita P, Urrego C. Cyclophosphamide-induced lupus flare in diffuse proliferative lupus nephropathy. Nefrologia 2011;22;31.
2. Ho A, Barr SG, Magder LS, Petri M. A decrease in complement is associated with increased renal and hematologic activity in patients with systemic lupus erythematosus. Arthritis Rheum 2001; 44:2350-7.
3. Finke D, Randers K, Hoerster R, Hennig H, Zawatzky R, Marion T, et al. Elevated levels of endogenous apoptotic DNA and IFN-alpha in complement C4-deficient mice: implications for induction of systemic lupus erythematosus. Eur J Immunol 2007;37:1702-9.
4. Dall'era MC, Cardarelli PM, Preston BT, Witte A, Davis JC Jr. Type I interferon correlates with serological and clinical manifestations of SLE. Ann Rheum Dis 2005;64:1692-7.

S.J. Park[1], J.H. Kim[2], T.S. Ha[3], J.I. Shin[2]
[1] Pediatrics Department.
Ajou University School of Medicine.
Suwon (Republic of Korea).
[2] Pediatrics Department.
Yonsei University College of Medicine.
Seoul (Republic of Korea).
[3] Pediatrics Department.
Chungbuk National University College
of Medicine. Cheongju (Republic of Korea).
Correspondence: J.I. Shin
Pediatrics Department.
Yonsei University College of Medicine.
120-752, Seoul. Republic of Korea.
shinji@yuhs.ac

Flare lupic during induction with cyclophosphamide therapy in diffuse proliferative lupus nephropathy

Nefrologia 2011;31(5):609-10
doi:10.3265/Nefrologia.pre2011.Jul.11029

To the Editor,

With regards our scientific letter, "Cyclophosphamide-induced lupus flare in diffuse proliferative lupus nephropathy"[1] we would like to thank Park at al for their contribution, and their suggestions of the possible immunological mechanisms involved in a lupus flare. Although they question whether cyclophosphamide really induces the flare or whether other mechanisms are involved, we would like to clarify that the title of the English version "Cyclophosphamide-induced lupus flare" could lead readers to believe that we consider that treatment with cyclophosphamide induced the flare, however, we wanted to communicate exactly the opposite. Indeed, as was reflected in the "Discussion" section, cyclophosphamide treatment is the best immunosuppressive agent, with the best results in inducing remission in severe forms of lupus nephropathy (LN).[2] As Park at al have pointed out in their letter, the lupus flare may or may not occur after cyclophosphamide treatment. In our case, it was during the cyclophosphamide induction period (less than 15 days). The flare was confirmed following the first phosphamide dose. Therefore, after having dismissed several causes (renal vein thrombosis, infection, etc.), we brought another cyclophosphamide dose forward (the second dose was 1.5g), which caused clinical and biochemical improvements, and the patient went into remission. To date, the patient has not had any further flares. We would like to emphasise the importance of the cyclophosphamide administered: we used the Euro-Lupus Nephritis Trial regime, 500mg every 15 days.[3] In this patient the flare would have been earlier, since the relapse occurred less than 15 days with 1g of the first dose of cyclophosphamide. For that reason, before considering cyclophosphamide treatment to be ineffective, it is important to bear in mind the dose that has been administered. Finally, we must highlight that we did not consider for one moment that cyclophosphamide induced the lupus flare. Given an error in the English version, the English title should have been: *Flare lupic during induction with cyclophosphamide therapy in diffuse proliferative lupus nephropathy.*