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Editorial Comment

Vaccination in solid-organ transplantation candidates: time for a benefit/risk assessment

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In this issue of CKJ, Kaul *et al.* [1] report their experience regarding chicken pox infection after renal transplantation. They found that the overall incidence is around 1%, somewhat lower than previously reported [2]. One of the major questions raised by this report is the vaccination policy before transplantation. The importance of vaccination in solid-organ transplantation candidates has been emphasized because of the potential direct and indirect risk of infection or immunological complications and since some vaccines are contraindicated when patients are maintained on immunosuppression [3]. Furthermore, the use of new powerful drugs such as belatacept, rituximab, eculizumab or bortezomib may be associated with a higher incidence of infectious complications. In some cases, these complications are specific and vaccination is mandatory, e.g. antimeningococcemia vaccine and eculizumab treatment.

The question to be raised, therefore, may be which 'infectious preparation' should be used before transplantation, i.e. for solid-organ transplant candidates. Indeed, the timing of vaccination administration in relation to end-stage renal failure is a key determinant of immunogenicity. For example, in the KDIGO guidelines, the only suggestion regarding pre-transplantation concerns hepatitis B virus (HBV) vaccine, and they recommend a vaccination policy to be undertaken as early as possible [4].

Besides this classical specificity, the first question regards anogenital human papillomavirus (HPV) infections, which are associated with a substantial increased risk of developing cervical and anogenital cancers [5]. With the development of an HPV vaccine, some have advised the administration of this vaccine to females between 9 and 26 years who are candidates for solid-organ transplantation. Indeed, this recommendation has been added in the commentary of the Canadian Society of Transplantation in the 2009 Kidney disease: Improving Global Outcomes (KDIGO) guidelines [6]. Of note, HPV may also induce benign tumours of the cutaneous epithelia and can be detected in lesions of keratinised squamous epithelia with oncogene expression in a large proportion of lesions [7]. One may speculate that the future HPV vaccines may be helpful for the management of spinocellular carcinoma, a frequent complication after transplantation.

As stated in the manuscript in this issue of CKJ, varicella zoster vaccine may also be an interesting candidate for vaccination prior to transplantation. The Advisory Committee of Immunization Practices (ACIP) has given a vaccination recommendation specifically for 'persons anticipating immunosuppression' [8]. However, important limitations for this policy are the characteristics of the vaccine and the need for significant delay between vaccination and transplantation. Since the zoster vaccine is a live attenuated vaccine, this vaccine must be administered if the transplantation is not imminent because of the potential risk of disseminated viral spread. Authors have suggested that the zoster vaccine must not be administered if immunosuppressive drugs are to be given within 14 days or even 2 months [3].

Another potentially interesting target for vaccination is cytomegalovirus (CMV). The management of this life-threatening complication has been improved by the use of efficient prophylactic treatments [9]. However, this approach may carry the risk of late CMV infection episode and/or the development of drug-resistant viral strains. It is known that the values of viral load are moderated by pre-existing natural immunity even though the cellular immunity plays a major role in controlling the infection. A recent phase II trial has been reported in adults awaiting kidney or liver transplantation [10]. Vaccination by a cytomegalovirus glycoprotein-B vaccine before transplantation has demonstrated a significant increase of glycoprotein-B antibody titres after vaccination in both seronegative and seropositive recipients compared with a placebo group. Furthermore, glycoprotein-B antibody titres correlated inversely with duration of viraemia. The authors conclude that humoral immunity carries a significant role in the reduction of CMV viraemia. A vaccine has been tested in allogeneic haemopoietic stem cell transplantation [11]. The use of this vaccine before conditioning was associated with a reduction of the occurrence, recurrence and delay of CMV viraemia. It is probable that a Phase III trial will be conducted in the near future.

Finally, the use of new drugs may urge the need for a new strategy of infection prevention. Eculizumab gives a good paradigm of this matter. Eculizumab is a monoclonal antibody that targets complement factor C5 and blocks the activation of the terminal complement cascade [12]. Initially approved for the treatment of paroxysmal nocturnal haemoglobinuria, it has been recently approved for the treatment of atypical haemolytic uraemic syndrome (aHUS), or its recurrence after transplantation, and is currently being tested in the context of both acute and chronic humoral rejection [13]. It is known that vaccination against meningococcus C (Men C) is essential in

patients with dysfunction of the complement system, as induced by eculizumab. Indeed, Men C vaccination is mandatory before using eculizumab. Therefore, if a patient whose initial nephropathy is aHUS is referred for renal transplantation, specific vaccination has to be started and verification for protective antibody titres must be conducted. In a paediatric population, it has been reported that eculizumab may be an acceptable maintenance of protective serum bactericidal activity (SBA) titres after transplantation under immunosuppressive therapy [14]. However, as stated by the authors, it remains unclear whether serologically defined protective SBA titres mediate true protection from invasive meningococcal disease in an immunocompromised patient, particularly under treatment with a complement inhibitor.

Because of all these potential positive aspects of vaccination pre-transplantation, one may question the safety of this approach. Theoretically, there is a potential risk for the development and/or the stimulation of the production of anti-HLA antibodies which may, in the end, compromise the access to a grafted organ or be responsible for an increased risk of acute humeral rejection. However, we, among others, have found no increase of anti-HLA antibody titres after influenza vaccination in renal transplant recipients [15]. But contradictory results have been reported. It is known that environmental factors, including therapeutic vaccinations, may influence the strength and/or specificity of alloimmunity. In one study, Roddy *et al.* have prospectively evaluated the effects of vaccination or immunization on cellular alloimmunity using alloantibody reactivity [16]. The alloantibody responses were increased in 50% of the subjects even though the reported effects were heterogeneous and transient. This may suggest the need for serial immune monitoring of alloreactivity when immunizations are administered to potential transplant recipients. Another element is that the antibodies reactive to the immunizing agent did not cross-react with the detected alloantibodies, suggesting that the increase of alloimmune reactivity was most likely due to a non-specific adjuvant effect from the vaccine. This may raise the question of the use of an adjuvant in this context. The pandemic of influenza A (H1N1) introduces an interesting element. In heart transplant recipients, the H1N1 vaccination was associated with an increase of the incidence of severe acute cellular rejection ($\geq$grade 2, 1990 ISHLT criteria) with the recent H1N1 viral antigen and adjuvant vaccination being the only risk factors associated with acute cellular rejection on multivariate analysis [17].

In summary, besides the specific question of VZV infection, the article presented in the current issue of the journal also questions our current strategy for infection prevention using vaccination prior to transplantation. We recommend that the safety of such a strategy has to be evaluated by careful monitoring of the efficacy on antibody titres and on the prevention of clinical infection, but also for alloimmune reactivation.

Conflict of interest statement. None declared.

(See related article by Kaul *et al*. Chickenpox infection after renal transplantation. *Clin Kidney J* 2012; 5: 203–206)

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