LETTER TO THE EDITORS

Multitarget anti-EBV therapy to prevent primary infection in kidney transplant recipients from deceased donor, at risk of post-transplantation lymphoproliferative disorder (EBV D+/R−)

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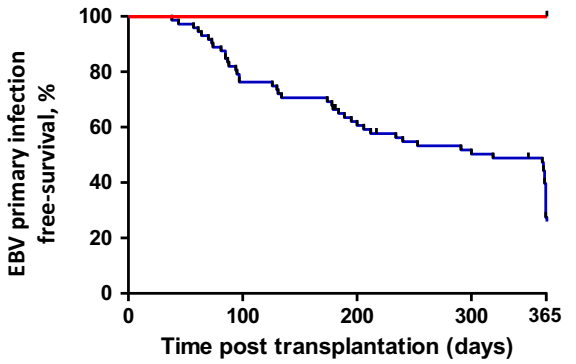
Dear Editors,

If all immunocompromised patients can experience post-transplantation lymphoproliferative disorder (PTLD) due to EBV reactivation, EBV-seronegative recipients in which primary infection can occur are at higher risk of developing PTLD when transplanted with an organ from an EBV seropositive donor [1,2]. In our center, among 73 EBV-seronegative adult patients transplanted between 2000 and 2016 (3% of the whole), eight developed an early PTLD and five others beyond one year, all EBV-related [3]. EBV is most often latent and inaccessible within B cells, but occasionally it achieves a lytic infection, susceptible to some antiviral drugs, such as (val)ganciclovir, and specific antibodies. Contrasting results exist regarding the effectiveness of antivirals and IVIG (polyclonal immunoglobulins that contains anti-EBV antibodies), to prevent PTLD in EBV-seronegative recipients [4–6]. More recently, Schachtner et al, in an attempt to prevent EBV transmission, treated five kidney transplant recipients (KTRs) from living donor with a single dose of rituximab (anti-CD20 antibody that depletes B cells[7]) one month before the transplantation[8]. In a similar intent in KTRs from deceased donors, we developed a protocol combining these different approaches. Indeed, while the precise mechanisms of EBV transmission from donor to recipient are still largely unknown, some clues suggest that both latently infected B cells and the lytic phase are involved. Furthermore, a single dose of rituximab does not deplete all B cells in secondary lymphoid organs [9], but could remove donor B cells latently infected. Patients were treated with a single dose of rituximab (375 mg/m^2 IV, day 0 post-transplantation), antiviral drugs (valganciclovir 450 mg twice daily, 6 months), and IVIG (0,4 g/kg on day 0 and 1). Patients received basiliximab as induction therapy and tacrolimus (though level between 6 and 8 ng/l) combined with acid mycophenolic (720 mg twice a day). Beyond clinical follow-up, EBV monitoring consisted of EBV viral load measurement every 6 weeks for 6 months and then every 3 months until one-year post-transplantation and EBV serology at 6 and 12 months post-transplantation. Positive DNAemia and/or seroconversion defined EBV primary infection. We treated 4 EBV-seronegative KTRs



No at risk	73	57	43	35	19
Nb of event	0	16	28	36	51

No at risk	4	4	4	4	4
Nb of event	0	0	0	0	0

Figure 1 Percentage of EBV primary infection defined as positive EBV DNAemia and/or EBV seroconversion, during the first year post-transplantation. Line blue shows 73 recipients EBV-seronegative transplanted between 2000 and 2016 (blue line) and line red 4 other treated with multitarget anti-EBV therapy (rituximab 375 mg/m^2 IV, day 0 post-transplantation; valganciclovir 450 mg twice daily, 6 months; polyclonal immunoglobulin 0,4 g/kg on days 0 and 1).

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from deceased EBV-positive donor. Their age ranged from 22 to 80 years, none were immunized, and tolerance of rituximab was good, except for one patient who developed CMV disease and BK viremia, all had excellent renal function at one year post-transplantation (ranging from 50 to 99 ml/min/1.73 m^2). As shown in Fig. 1, during the first year post-transplantation, while in our historical group 73% of patients experienced EBV primary infection and 11% developed PTLD, none of the 4 patients had either EBV primary infection or PTLD. At the last follow-up ranging from 24 to 36 months, no one has developed PTLD. Even if EBV monitoring cannot formally rule out a primary infection because EBV DNAemia and possibly seroconversion can be transient [10], our observation suggests that a multi-target anti-EBV therapy with a good safety profile consisting of a single dose of rituximab with antiviral drugs and IVIG prevents the transmission of EBV from the deceased donor to the recipient and consequently EBV-related PTLD. While the number of patients is of course too limited to conclude, a multicenter randomized trial funded by the French government (PHRC REPLY) will soon test the efficacy of prophylactic rituximab in adult EBV-negative KTRs on incidence of EBV primary infection and PTLD.

Conflicts of interest

The authors have declared no conflicts of interest.

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