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INVITED COMMENTARY

Dealing with EBV sero-negative recipients: copy paste the CMV recipe?*

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A negative sero-status for Epstein–Barr virus (EBV) is not such a rare event among kidney recipients. According to the Collaborative Transplant Study it occurs overall in 12% of the cases [1]. Not surprisingly the proportion is higher in children and young adults; nevertheless 1 in 10 adults still has no evidence of previous immunization against EBV at transplantation.

Why is it so important to define special strategies for EBV sero-negative recipients?

The main risk is the subsequent development of EBV-related post-transplant lymphoproliferative disorder (PTLD). This association is well known but was recently re-examined by the Registry of Transplant Recipients in the United States. The analysis confirmed the higher risk of PTLD for D+/R− with adjusted hazard ratios up to 3.58 for kidney transplants [2].

In transplantation settings the lytic replication phase of EBV in epithelial cells is usually not the matter of concern but the latent infection of B cells. If the latent B cell infection takes place under immunosuppression, the development of a controlling immune response is impaired. It may lead to inadequate production of EBV-specific CD4 and CD8 T cells and open the way to uncontrolled B-cell replication.

The latent EBV infection is characterized by the persistence of the viral genome in B cells and the expression of restricted latent gene products which can drive cell proliferation. The latent infected cells are furthermore protected

against apoptosis. After transplantation, a disruption in the balance between viral escape mechanisms and the immune response may lead to reactivation of the transformed B cells, ending in the dramatic occurrence of PTLD.

Which are the options for EBV-negative recipients?

One possibility is to match EBV sero-negative donors with similar recipients. However, due to the low proportion in the general population, the chance is limited. In Switzerland, according to Swisstransplant data collected since 2007, the overall proportion of sero-negative kidney recipients reached 2.3% and 8% for kidney donors, more so if the donors were <20 years old [Swisstransplant, unpublished data]. Due to a priority in organ allocation 29% of the sero-negative recipients were attributed a kidney from a sero-negative donor. A recent analysis of the UNOS data looking at the effect of EBV sero-status on the occurrence of PTLD in kidney transplants showed a hazards ratio for PTLD in the D−/R− constellation nearly three times lower than in the D+/R− constellation [3].

Because the viral load per se is a risk factor for the transformation of B cells, another option is the monitoring of the EBV viremia with adjustment of the immunosuppression accordingly [4]. This option may however increase the rejection rate. Monitoring peripheral B-cell lymphoproliferation through CD19-positive cells in flow cytometry has also been advocated [5].

How does the present study (Höcker *et al.*) contribute to this issue?

The study by Höcker *et al.* [6] suggests managing EBV sero-negative donors with a prophylaxis. Prophylaxis is efficient in the early lytic phase of the viral infection. It decreases viremia, which in turn decreases the risk of B-cell transformation. Similarly to a study in paediatric liver recipients, an EBV high-risk constellation without intervention leads to a primo-infection in 80% of the cases [7].

The early 1980s marked the first reports on inhibitory effect of gancyclovir and acyclovir on EBV replication [8]. Gancyclovir was found superior to acyclovir with the particularity to be active in the initial lytic phase of the infection. From the mid-1990s, reports were published about prevention and pre-emptive therapy with both gancyclovir and acyclovir for liver, kidney and pancreas recipients under various immunosuppressive regimens [4,5,9]. None of these series was large, multi-centric or even randomized. Nevertheless, compared to historical recipients without prophylaxis, the overall incidence of PTLD was reduced under prophylaxis up to 50% or more, while the high-risk constellation D+/R− in paediatric patients showed the highest profit.

Against this background, Höcker *et al.* report a prospective multi-centric study. This observational study focuses on the 1 year outcome and primary EBV infection in high-risk D+/R− kidney recipients.

No randomization was performed and this remains a weakness of the study. However, as stated by the authors themselves, a randomisation would not have been possible. The proportion of EBV-negative recipients in high-risk situations is limited. Furthermore, among this subgroup, many require chemoprophylaxis anyway due to concomitant cytomegalovirus (CMV) risk constellation. Thus over 6 years all EBV high-risk kidney recipients of 10 German paediatric centres were included in the analysis. The 28 patients received either prophylaxis with gancyclovir or valgancyclovir or no prophylaxis. The assignment to the prophylaxis or control group was primarily, although not exclusively, based on the indication for concomitant CMV risk constellation.

The results show that any prophylaxis reduced *de novo* viremia in the first year post-transplant. If primary infection occurred it did so after completing the prophylaxis; none occurred beyond 6 months. Prophylaxis decreased both the incidence and the intensity of the primary infection as measured by viremia. Unfortunately, these positive effects did not translate into a clear reduction of PTLD. It can be argued that the study was not focusing on PTLD as such, had a too short follow-up and a too small collective to establish statistical significance. Nevertheless, PTLD occurred in 5% in the prophylaxis group and 12.5% in the control group and it would be interesting to observe the trend over a longer follow-up period.

Despite its limitations, this study represents an interesting effort to establish a basis for a larger consensus on prophylaxis as a management of EBV-negative recipients in high-risk constellations. This could prove a milestone for approval of the use of chemoprophylaxis for EBV and not only CMV.

However, the study also raises questions for which a follow-up update would be highly interesting: Does the viremia remain negative in both groups after the first year? Will the PTLD incidence remain lower in the prophylaxis group over time and will prophylaxis also influence the occurrence of late-onset PTLD? Would a prolonged prophylaxis during 6 months confer a further advantage regarding the incidence of primary infection and height of viremia?

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