To the editor:

Monitoring of EBV reactivation is justified in patients with aplastic anemia treated with rabbit ATG as a second course of immunosuppression

Recently Scheinberg et al[1] reported their findings on cytomegalovirus (CMV) and Epstein-Barr virus (EBV) reactivation following antibody-based immunosuppressive regimens in patients with severe aplastic anemia. Although in the majority of patients EBV reactivation was observed, no EBV-related disease was observed; therefore the authors conclude that there is no need to routinely monitor viral reactivation in these patients. We generally agree with that; however, in some patients monitoring reactivation of EBV might be necessary, which is supported by the following case report describing a patient with severe aplastic anemia (SAA) being treated with rabbit antithymocyte globulin (ATG) and cyclosporin, developing life-threatening EBV-related lymphoma.

A 42-year-old EBV seropositive woman with SAA who did not respond to previous treatment with horse antithymocyte globulin (40 mg/kg for 4 days) and cyclosporine, was treated with rabbit antithymocyte globulin (12.5 mg/kg for 4 days) and cyclosporine 10 months after the horse-ATG. Two weeks later she was admitted with fever, a painful throat, minor enlarged submandibular, axillary, and inguinal lymph nodes, and hepatosplenomegaly. Laboratory investigations showed hemoglobin (Hb) 7.0 g/dL (4.4 mM), thrombocytes 6×10^9/L, leucocytes 2.2×10^9/L, of which 76% were lymphocytes, no fragmentocytes, creatinine 226 μM, and LDH at 811 U/L. She rapidly deteriorated and needed dialysis and mechanical ventilation. Biopsy of an inguinal lymph node showed an EBV-associated diffuse large B-cell lymphoma expressing LMP-1 (latent membrane protein), EBER, and EBNA-2 (EBV nuclear antigen). Polymerase chain reaction (PCR) of peripheral blood showed 4×10^6 EBV-DNA copies/mL. To restore T-cell function, cyclosporine was discontinued, but because urgent treatment of her lymphoma was required, rituximab (375 mg/m^2) was administered at the intensive care unit. Because of persisting hepatosplenomegaly and stagnant EBV copies after 2 treatments with rituximab, cyclophosphamide was added (750 mg/m^2), leading to clinical improvement and disappearance of circulating EBV copies. At this moment, 2 years later, her blood counts are improved, without the need for immunosupressive therapy. No EBV reactivation or recurrent lymphoma occurred.

In contrast to the series by Scheinberg, in our patient, reactivation of EBV did lead to severe clinical disease. This might be partly related to the higher dose of rabbit ATG we administered, but it can be well explained by the observation of Scheinberg that all patients receiving rabbit ATG showed reactivation of EBV, with median peaks of viral loads being 60-fold higher and the median duration of PCR positivity almost 2-fold longer compared with horse ATG. The authors suggest that rabbit ATG is more immunosuppressive, supported by the longer duration of lymphopenia they observed. However, a relation with its administration as a second course of ATG could not be excluded.

Therefore, we suggest monitoring EBV reactivation in patients being treated with rabbit ATG as a second course of immunosuppression. These patients probably benefit from early detection of reactivation, considering that a continuous rise in EBV DNA load was indicative of imminent disease in T-cell–depleted allogeneic transplantations, which was not observed after non–T-cell–depleted allogeneic transplantations.[2] This confirms the hypothesis of Schein-berg that progression of disease correlates with the inability to generate an effective immune response. Whether in the non–transplantation setting EBV-reactivation justifies preemptive treatment with rituximab[3] or should lead to watchful waiting, as the data of Scheinberg suggest, needs to be determined.[1,4]

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Response

EBV reactivation in the immunosuppressed: to treat or not to treat?

Wondergem et al raise the issue that in certain patients with aplastic anemia treated with immunosuppressive therapy, Epstein-Barr virus (EBV) reactivation may sometimes transcend a subclinical stage and progress to an EBV-lymphoproliferative process. In our paper, the intention was to suggest that monitoring EBV and cytomegalovirus (CMV) viral load is not necessary for patients treated with standard immunosuppressive protocols, but with novel immunosuppressive schedules, more potent immunosuppressive agents or repeated treatments, an increased awareness of EBV (and CMV) disease is warranted.

Indeed, our study of prospective EBV monitoring was initiated because of a case similar to the one described by Wondergem et al. Our patient was a 32-year-old man with severe aplastic anemia who received horse antithymocyte globulin (ATG) with no response at 3 months and was then treated with rabbit antithymocyte globulin. Two weeks later, rapidly progressive massive lymphadenopathy developed in the neck, axillary, and mediastinal areas, requiring endotracheal intubation. Axillary lymph node biopsy revealed EBV lymphoproliferation, accompianied by an EBV viral load of 870 000 copies per 10^6 mononuclear cells in the blood. Cyclosporine was discontinued and the patient received one cycle of cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R) with a rapid decrease in node size and in peripheral blood EBV copy numbers. He went on to unrelated hematopoietic stem cell transplantation for his aplastic anemia and 4 years later he is doing well with no further evidence of EBV disease.

Notwithstanding, EBV-lymphoproliferative disease after immunosuppression for aplastic anemia is very rare and its occurrences have been limited to case reports. We have now monitored EBV reactivations in more than 150 courses of immunosuppressive therapy with no additional cases of EBV disease, despite very high viral loads and prolonged periods of EBV polymerase chain reaction (PCR) positivity. In the past 18 months we have monitored EBV viral loads in patients who received rabbit ATG as initial therapy; higher viral loads were again observed in patients treated with the rabbit ATG up-front (similar levels to what was reported in the manuscript when rabbit ATG was administered as a second course only) compared with those who received horse ATG. Therefore, the EBV viral load cannot be interpreted in isolation as cut-off values that are predictive or diagnostic of disease have not been established. Rather than mandate routine testing for what we believe is a rare event, we would instead prefer to stress awareness of the potential for EBV reactivation and disease, with intervention only when there is clinical suspicion due to rising lactate dehydrogenase (LDH), lymphadenopathy, clinical deterioration in association with a high EBV viral load, and confirmatory lymph-node histology.

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To the editor:

Physical and not mental health is impaired in very long-term survivors after HSCT compared with their respective donors: a paired analysis

Bhatia and colleagues[1] recently published a comprehensive analysis on late mortality after allogeneic hematopoietic stem cell transplantation (HSCT), providing interesting data about the functional status of 547 recipients and 319 siblings. At the time of this Collaborative Bone Marrow Transplant Survivor Study, patients and donors had a median age of 41.5 and 44 years, respectively, and a median time of 8.6 years after HSCT. By questionnaire, long-term survivors reported significantly more difficulties in integration back into society after HSCT, in holding down employment, or in obtaining or retaining health insurance compared with their siblings. These results provided additional information to the relatively scarce and partially conflicting reports on functional status in the long-term recipients of HSCT surviving more than 10 years.[2,3]

In order to obtain a comprehensive overview on physical and mental health in very long-term survivors after HSCT, we invited 44 recipients and their respective HLA-identical sibling donors to take part in a prospective study at the University Hospital of Basel. Both the recipients and their donors were controlled at the same time point, in pairs, and were given a complete clinical and biologic examination. Each answered a Short Form 36 (SF-36) Health Survey,[4,5] which provides the generic health status measure using 36 items assessing 8 different concepts (Table 1). Three of the concepts provide a score for physical health, 3 for mental health, and 2 for general health status. These 8 concepts are summarized in 2 global tests, one for physical and one for mental health. Norm-based scores were used, in which 50 represents the mean score, and 10 the standard deviation for the general population. The median age of the recipients and donors at time of the study was 44.3 years (24-63) and 43.4 years (22-61), respectively, with a median time of 17.5 years (range, 11-26 years) after HSCT. Four patients received an HSCT for aplastic anemia and 40 for hematologic malignancies. All patients received bone marrow as stem cell source and total body irradiation was part of the conditioning in 39 patients (89%). Acute graft-versus-host disease (GVHD) was observed in 31 (70%), and chronic GVHD in 22 (50%) patients.

In a paired comparison, recipients showed a significantly lower rank of the norm-based scores for all questions related to physical well-being, except for role limitation, but no difference in the mental health scores compared with their respective donors (Table 1). This is confirmed by the global test for physical ($P = .001$) and mental ($P = .831$) health. Physical health was significantly lower in patients with extensive chronic GVHD ($P = .05$), in females ($P = .024$), in recipients older than 25 years at HSCT ($P = .024$) or older than 42 years at study evaluation ($P = .05$). None of these factors had an impact on mental

Table 1. Short Form 36 Health Survey: Paired comparison between recipients and their respective donor

Items	Donor*	Recipient*	*P*
Items describing physical health			
Physical functioning	54.7	50.9	.001
Role limitations due to physical health	54.6	52.3	.213
Bodily pain	59.2	54.9	.042
Items describing general health (physical and mental)			
General health perception	57.0	50.7	.001
Vitality	65.4	52.3	.039
Items describing mental health			
Social functioning	54.0	51.2	.324
Role limitations due to emotional problems	53.9	51.0	.285
Mental health	52.7	50.9	.638
Global tests			
Physical Component Summary (PCS)	57.1	52.8	.001
Mental Component Summary (MCS)	52.9	50.8	.831

* Numbers are means of norm-based scores.