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Current preventive strategies and management of Epstein–Barr virus-related post-transplant lymphoproliferative disease in solid organ transplantation in Europe. Results of the ESGICH Questionnaire-based Cross-sectional Survey

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Abstract

There is limited clinical evidence on the utility of the monitoring of Epstein–Barr virus (EBV) DNAemia in the pre-emptive management of post-transplant lymphoproliferative disease (PTLD) in solid organ transplant (SOT) recipients. We investigated current preventive measures against EBV-related PTLD through a web-based questionnaire sent to 669 SOT programmes in 35 European countries. This study was performed on behalf of the ESGICH study group from the European Society of Clinical Microbiology and Infectious Diseases. A total of 71 SOT programmes from 15 European countries participated in the study. EBV serostatus of the recipient is routinely obtained in 69/71 centres (97%) and 64 (90%) have access to EBV DNAemia assays. EBV monitoring is routinely used in 85.9% of the programmes and 77.4% reported performing pre-emptive treatment for patients with significant EBV DNAemia levels. Pre-emptive treatment for EBV DNAemia included reduction of immunosuppression in 50.9%, switch to mammalian target of rapamycin inhibitors in 30.9%, and use of rituximab in 14.5% of programmes. Imaging by whole-body 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) is used in 60.9% of centres to rule out PTLD and complemented computer tomography is used in 50%. In 10.9% of centres, FDG-PET is included in the first-line diagnostic workup in patients with high-risk EBV DNAemia. Despite the lack of definitive evidence, EBV load measurements are frequently used in Europe to guide diagnostic workup and pre-emptive reduction of immunosuppression. We need prospective and controlled studies to define the impact of EBV monitoring in reducing the risk of PTLD in SOT recipients.

Keywords: Epstein–Barr virus, Europe, post-transplant lymphoproliferative disease, pre-emptive treatment, survey
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Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a feared complication after solid organ transplantation (SOT), occurring

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in 1–30% of recipients [1–3] with an overall mortality that may be as high as 50% [4,5].

Most cases of PTLD have been associated with Epstein–Barr virus (EBV), mostly in patients undergoing primary EBV infection after transplantation [6]. Whereas treatment of advanced PTLD typically requires chemotherapy, early polyclonal or oligoclonal stages may initially respond to reduced immunosuppression combined with rituximab therapy and therefore the possibility of pre-emptive treatment has received considerable attention. In haematopoietic stem cell transplant recipients surveillance of EBV DNAemia by quantitative nucleic acid testing (QNAT) has been used to identify patients at risk for PTLD development [7–9]. However, the clinical evidence supporting EBV DNA monitoring in SOT recipients is limited [10] and, although major advances have been made in the incorporation of QNAT-based EBV detection techniques in clinical microbiology laboratories, there is no consensus on optimal techniques, the best monitoring timing, or the most accurate cut-offs in viral load indicating high risk for PTLD development [11–13]. The objective of the present study was to evaluate the current practices with respect to EBV-associated PTLD in SOT recipients in Europe through a survey conducted on behalf of the ESCMID Study Group of Infection in Compromised Hosts (ESGICH) and directed to all the European SOT centres.

Materials and methods

The study design was a questionnaire-based cross-sectional survey performed on behalf of the ESGICH from the ESCMID. We contacted the different potentially active SOT programmes (including kidney, pancreas/kidney–pancreas, liver, heart, lung and intestinal transplants) through registries accessed in websites from different governmental or scientific organizations, depicted in the Supporting information (Appendix S1). To find the e-mail address of each SOT programme representative, apart from the contact e-mails provided in the different registries we also searched those included in PubMed published studies performed in these centres from 2008 to 2013. More e-mail contacts of virologists and Transplant Infectious Diseases (TID) specialists eventually involved in the management of PTLD were requested from these initially selected transplant centres. The survey was carried out between 1 and 30 June 2013. An e-mailed invitation and a weekly reminder with a summary of the project and a personal link to an internet questionnaire service provider (https://es.surveymonkey.com/) was sent to all the representatives. The basal module of the survey consisted of a total of 26 'hot topics' questions related to the prevention of EBV-related PTLD that had been previously proposed and reviewed through a panel of experts of ESGICH (Supporting information, Appendix S2). A complementary survey module was designed for virologists that included some more specific questions with respect to the basal module (Supporting information, Appendix S3).

We arbitrarily defined high-risk EBV DNAemia as one or more of the following: (1) high-level DNAemia (above the 90th centile of values obtained in the laboratory) (2) increasing DNAemia (more than tenfold or >1 log10 copies (cp)/mL in two consecutive determinations), and (3) persistent DNAemia (persistence of EBV DNAemia in at least two consecutive determinations separated by at least 3 months).

The study was approved by the specific scientific Committee of the European Society of Clinical Microbiology and Infectious Diseases. Requests for authorization by the ethics committees of each centre were not considered necessary because this was a survey that simply collected the opinions of transplant physicians, and it did not involve approaching patients directly or seeking any patient-specific data.

Statistical methods

A database including all the responses of the participants was provided by the internet questionnaire service for further analysis. Continuous variables were expressed as the mean for those with a normal distribution, and as the median (mostly for those with a skewed distribution). Discrete variables were expressed as percentages. Student's unpaired *t*-test was used to compare continuous variables, the Mann–Whitney *U*-test to compare continuous variables with non-normal distribution, and the chi-square or Fisher exact test to compare proportions. All statistical tests were two-tailed and the threshold of statistical significance was $p < 0.05$. The statistical software SPSS (SPSS 15.0, Inc., Chicago, IL, USA) was used to perform the calculations of the different analyses.

Results

An invitation for participating in the survey was sent by e-mail to 669 physicians representing 669 SOT groups from 35 European countries.

A total of 71 transplant physicians (TP) representatives of SOT groups from 15 European countries finally participated in the study which supposed a global participation of 10.5%. As is shown in Table 1, all the types of SOT were represented in the survey and the percentage of participation varied from 24.5% in lung transplant to 4% in pancreas transplant programmes. Spain and Italy were the most represented countries (participation of

TABLE 1. Participation in the survey of European solid organ transplant groups

	Survey proposal	Accepted participation	% participation
Per type of transplant group			
Lung transplant	53	13	24.5%
Bowel transplant	31	4	12.9%
Liver transplant	107	13	12.1%
Renal transplant	285	30	10.5%
Heart transplant	96	7	7.3%
Pancreas transplant	97	4	4.1%
Per country of origin			
Slovenia	2	2	100%
Spain	81	20	24.7%
Italy	120	23	19.2%
Czech Republic	10	2	20.0%
Switzerland	17	3	17.6%
France	92	7	7.6%
Belgium	29	2	6.9%
Germany	117	4	3.4%
United Kingdom	76	2	2.6%
Other	125	6	4.8%
TOTAL	**669**	**71**	**10.5%**

24.7% and 19.2%, respectively). Additionally, from the total of 47 TID consultants and 28 virologists contacted, through responding transplant physicians, 17 (36.2%) and 13 (46.4%) participated, respectively.

Characteristics of participating SOT centres

As shown in Table 2, the majority of the participants were highly experienced adult transplant groups (nearly 90% with transplant programmes with experience over 10 years) and with a high transplant activity. EBV serostatus of the recipient was routinely recorded in 69 centres (97%) and 64 (91%) had quantitative EBV DNAemia measurements in place.

TABLE 2. Characteristics of the 71 European SOT programmes participating in the survey

Type of transplant, *n* (%)	
Kidney	30 (42.3)
Liver	13 (18.3)
Heart	7 (9.9)
Lung	13 (18.3)
Pancreas	4 (5.6)
Small bowel	4 (5.6)
Paediatric transplant, *n* (%)	9 (13.2)
Experience of the SOT programme, *n* (%)	
>20 years	46 (64.8)
16–20 years	9 (12.7)
11–15 years	7 (9.9)
5–10 years	8 (11.3)
<5 years	1 (1.4)
Number of transplants performed in 2012, median (range)	
Kidney	62 (10–199)
Liver	40 (16–87)
Heart	18 (11–33)
Lung	17 (2–115)
Pancreas	3 (2–12)
Small bowel	47 (4–88)
Routine determination of EBV serostatus, *n* (%)	
Recipient	69 (97.2)
Donor	54 (76.1)
EBV DNAemia determination available at the Transplant centre, *n* (%)	64 (90.1)

Abbreviations: EBV, Epstein–Barr virus; SOT, solid organ transplantation.

Preventive measures guided by clinical risk factors

As shown in Table 3, EBV serological mismatch is perceived as the major risk factor for PTLD development in 71.8% of surveyed TP, followed by the use of lymphocyte-depleting treatments (15.5%). Thirty-eight TP reported the use of preventive measures in patients with clinical high-risk factors, irrespective of EBV DNAemia monitoring, including the use of valganciclovir in 11.3% of transplant programmes, and the change of immunosuppression from calcineurin inhibitors to mammalian target of rapamycin inhibitors (m-TORi) in 12.7% of the transplant groups. Compared with TP, only 11.8 of surveyed TID specialists supported implementation of such measures (p 0.08) exclusively through the use of valganciclovir.

Preventive measures against PTLD based in EBV-DNAemia monitoring

As shown in Table 4, 55 of the 64 centres (85.9%) with QNAT techniques in place performed some kind of EBV surveillance. Although nearly 40% reported performing EBV load surveillance in patients with clinical suspicion of PTLD, 34.4% of the centres perform EBV load surveillance in all SOT recipients: 16.6% and 18.2% in liver and heart transplant, 33% and 38% in pancreas and renal transplant, and 45.4% and 50% in lung and intestinal transplant, respectively. TID specialists were more likely to restrict EBV surveillance to selected high-risk patients than TP (43.8% versus 12.5%, p 0.01), and only 12.5% of TID consultants favour the use of universal EBV surveillance.

The majority of TP (77.4%) use preventive measures in patients with high-risk EBV DNAemia, such as the reduction of immunosuppression (50.9%), and the conversion to m-TORi (30.9%). Up to 14.5% affirmed that they had used rituximab for this indication and 7.3% even indicated the use of immune-adoptive T-cell therapy. In any case, inclusion of such preventive measures in transplant procedure institutional protocols was less reported, only in 18.2% of the centres.

Indication of a whole-body computed tomography (CT) prompted exclusively by high-risk EBV DNAemia was reported in 7.8% of the centres overall, and it was recommended by 31.3% of the TID representatives (p 0.03).

TABLE 3. Prevention of PTLD independently of EBV DNAemia determination

	Transplant physicians *n* = 71	Infectious disease consultants *n* = 16	p value[a]
Which is the major clinical risk factor for PTLD?, *n* (%)			
Use of lymphocyte-depleting treatments	11 (15.5)	1 (5.9)	
Seronegative EBV recipient with a seropositive EBV donor	51 (71.8)	15 (88.2)	
Type of transplanted organ	3 (4.2)	0	
No specific risk factors have been reported	6 (8.5)	1 (5.9)	
Have you used preventive measures in patients with high clinical risk factors?, *n* (%)			
At least one preventive measure	27 (38)	2 (11.8)	0.08
Oral acyclovir	2 (2.8)	0	
Oral valacyclovir	4 (5.6)	0	
Intravenous ganciclovir	2 (2.8)	0	
Oral valgancyclovir	8 (11.3)	2 (11.8)	
Change immunosuppression to mammalian target of rapamycin inhibitors	9 (12.7)	0	0.2

Abbreviations: EBV, Epstein–Barr virus; PTLD, post-transplant lymphoproliferative disease.
[a]Only p values <0.5 are shown.

TABLE 4. Preventive measures against PTLD based in EBV DNAemia monitoring

	Transplant physicians	Infectious disease consultants	p-value[a]
Any kind of monitoring of EBV DNAemia in SOT?, *n* (%)	***n* = 64**	***n* = 16**	
U/NA	2 (3.1)	0	
No, never.	7 (10.9)	0	0.37
Only in patients with suspicion of established PTLD	25 (39.1)	7 (43.8)	
Only in SOT at high risk for PTLD	8 (12.5)	7 (43.8)	0.01
Yes, in all SOT recipients.	22 (34.4)	2 (12.5)	0.16
Any kind of EBV DNAemia monitoring	55 (85.9)	16 (100)	0.22
Experience on preventive measures directed by EBV DNAemia determination, *n* (%)	***n* = 55**[b]	***n* = 16**	
At least one preventive measure	31 (77.4)	9 (56.3)	0.18
Acyclovir/Valacyclovir	5 (9.1)	1 (5.9)	
Ganciclovir/valganciclovir	7 (12.7)	1 (5.9)	
Reduction of IS	28 (50.9)	5 (29.4)	0.22
Change IS to m-TORi	17 (30.9)	6 (35.3)	
Rituximab	8 (14.5)	2 (11.8)	
Immuno-adoptive therapy	4 (7.3)	1 (5.9)	
Protocolized preventive measures directed by EBV DNAemia determination, *n* (%)	***n* = 55**[b]	***n* = 16**	
At least one preventive measure	10 (18.2)	1 (6.3)	0.44
Acyclovir/Valacyclovir	1 (1.8)	0	
Ganciclovir/valganciclovir	4 (7.3)	0	
Reduction of IS	7 (12.7)	0	
Change IS to m-TORi	4 (7.3)	0	
Rituximab	3 (5.5)	0	
Immuno-adoptive therapy	1 (1.8)	0	
Other	0	1 (6.3)	
Total body CT for PTLD evaluation in patients with high-risk EBV DNAemia?, *n* (%)	***n* = 64**	***n* = 16**	
U/NA	6 (9.3)	0	
No	9 (14.1)	0	0.2
Only when clinical and/or analytical data suggestive of PTLD	44 (68.7)	11 (68.8)	
Yes, in the majority of patients with high-risk EBV DNAemia	5 (7.8)	5 (31.3)	0.03
Use of FDG-PET whole-body for PTLD evaluation in patients with high-risk EBV DNAemia?, *n* (%)	***n* = 64**	***n* = 16**	
U/NA	6 (9.4)	0	
It is protocolized for PTLD evaluation in patients with high risk of PTLD	7 (10.9)	2 (12.5)	
Sometimes, complementary to CT	32 (50)	12 (75)	0.13
We have no experience in this indication.	19 (29.7)	2 (12.5)	0.28
Biopsy of the graft for PTLD evaluation in patients with high risk EBV DNAemia?: n (%)	***n* = 64**	***n* = 16**	
U/NA	6 (9.4)	0	
No	16 (25)	3 (18.8)	
Only when clinical data suggestive of PTLD	39 (61)	13 (81.3)	0.22
Yes, in the majority of patients with high risk EBV DNAemia	3 (4.7)	0	
Lymphatic node biopsy for PTLD evaluation in patients with high-risk EBV DNAemia?: n (%)	***n* = 64**	***n* = 16**	
U/NA	6 (9.4)	0	
No	12 (18.8)	0	0.14
Only when clinical/radiological/analytical data suggestive of PTLD	42 (65.6)	16 (100)	0.01
Yes, in the majority of patients with high risk EBV DNAemia	4 (6.3)	0	

Abbreviations: CT, computed tomography; EBV, Epstein–Barr virus; FDG-PET, 18-fluoro-deoxyglucose positron emission tomography; IS, immunosuppression; m-TORi, mammalian target of rapamycin inhibitors; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplantation; U/NA, Unknown/No answer.
[a]Only p values <0.5 are shown.
[b]Subgroup of centres performing EBV DNAemia monitoring.

Experience of whole-body 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) as a diagnostic tool for discard PTLD was reported in 60.9% of surveyed centres (in 50% complementary to CT) and it was included in protocols of diagnostic workup in patients with high-risk EBV DNAemia in 10.9% of them. However, one-third of the transplant centres did not report any experience with FDG-PET. Invasive diagnostic measures such as allograft biopsy or lymphatic node biopsy were generally performed only in patients with clinical manifestations compatible with PTLD (61% and 65.6%, respectively).

To test the effect of the characteristics of the different centres in the answers regarding preventive measures against PTLD based in EBV DNAemia monitoring we analysed the results stratified by transplant activity in the previous year (40 centres with a number of transplants below the 50th centile and 31 above this value) and we did not find any statistically significant differences among both groups.

We also compared the results between the nine centres for paediatric transplants and 62 adult transplant programmes. Universal monitoring of EBV DNAemia was reported significantly more frequently in paediatric transplant than in adult transplant programmes (78% versus 27%; p 0.01) as were the use of preventive measures guided by EBV DNAemia (89% versus 44.7%; p 0.02). Interestingly, the report of the use of rituximab as pre-emptive therapy was also significantly more frequent in paediatric transplant programmes (62.5% versus 6.5%; $p < 0.0001$).

EBV DNAemia determination

We finally surveyed some general aspects of the QNAT techniques used for determining EVB DNAemia loads complemented by some more specific issues in the specific formularies directed to transplant virologists (Table 5). Commercial QNAT were the most frequently used assays, but at least 35.7% of the clinical virologists reported the use of laboratory-developed tests. Whole blood was the preferred clinical specimen in the majority of centres (45.5% reported by TP, 31.3% by TID and 57.1% by clinical virologists), and plasma specimens were used in a significant proportion of centres (29.1% TP, 50% TID consultants, and 35.7% clinical virologists).

We assumed that there is not a specific cut-off point and we asked which values were assumed to reflect 'high' DNAemia (defined in the formulary as those above the 90th centile). Interestingly, the values of DNAemia considered to be high were variable and depended on the PCR technique used. TP tended to consider lower EBV loads as 'high-risk' DNAemia (34.5% >1000 cp/mL and 12.7% >100 cp/mL) than did TID (37.5% >5000 cp/mL) or virologists (42.9% >10 000 cp/mL). It is noteworthy that virologists reported a high variability in the targets included in the PCR technique, and about 28.5% were not aware of this detailed aspect of the test. Further, 28.6% of virologists were unaware of the WHO experts committee recommendations published in 2011 [14] and only 57.1% had accessed the contents of the document.

TABLE 5. PCR assay for EBV DNAemia monitoring

	Transplant physicians	ID consultants	Virologist
Type of PCR technique, *n* (%)	***n* = 55**[a]	***n* = 16**	***n* = 14**
Unknown	13 (23.6)	1 (6.3)	0
Real-Time PCR commercial	38 (69.1)	7 (43.8)	9 (64.3)
Real-Time PCR laboratory-developed	4 (7.3)	8 (50)	5 (35.7)
Type of clinical sample for PCR determination, *n* (%)	***n* = 55**[a]	***n* = 16**	***n* = 14**
Unknown	11 (20)	3 (18.8)	0
Plasma	16 (29.1)	8 (50)	5 (35.7)
Separated mononuclear cells	3 (5.5)	0	1 (7.1)
Whole blood	25 (45.5)	5 (31.3)	8 (57.1)
Values of EBV DNAemia considered as high DNAemia?, *n* (%)	***n* = 55**[a]	***n* = 16**	***n* = 14**
U/NA	5 (9.1)	3 (18.8)	1 (7.1)
More than 100 cp/mL	7 (12.7)	1 (6.3)	1 (7.1)
More than 1000 cp/mL	19 (34.5)	3 (18.8)	2 (14.3)
More than 1500 cp/mL	4 (7.3)	2 (12.5)	1 (7.1)
More than 5000 cp/mL	11 (20)	6 (37.5)	3 (21.4)
More than 10 000 cp/mL	9 (16.4)	1 (6.3)	6 (42.9)
EBV PCR target included in the PCR technique, *n* (%)	**NA**	**NA**	***n* = 14**
Unknown	—	—	4 (28.5)
BALF5	—	—	1 (7.1)
*Bam*HI-W	—	—	1 (7.1)
BNRF1 P 143	—	—	3 (21.4)
BXLF1	—	—	3 (21.4)
EBNA-1	—	—	1 (7.1)
Others	—	—	1 (7.1)
Awareness of WHO expert Committee on standardization[b]**, *n* (%)**	**NA**	**NA**	***n* = 14**
No	—	—	4 (28.6)
I am aware but I have not accessed the contents	—	—	2 (14.3)
I have accessed the contents of the document	—	—	8 (57.1)

[a]Subgroup of centres performing EBV DNAemia monitoring.
[b]First WHO International Standard for Epstein–Barr Virus (EBV) for Nucleic Acid Amplification Technology (NAT)-Based Assays [14].

Discussion

The results of this pan-European survey offer a current picture of the attitude of the different groups of TP towards prevention of EBV-related PTLD. The majority of transplant group representatives were aware of the importance of EBV in the development of PTLD and they verified the widely accepted role of serological screening of recipient and donor [3,15–17]. Up to 40% of the groups acknowledged that some preventive measures are performed in high-risk patients, mostly represented by seronegative recipients from seropositive EBV donors. However, this position was extended by some to patients treated with lymphocyte-depleting treatments, a condition that has also been related with an added risk in some studies [5,15,18–20].

The most frequently reported preventive measures applied in high-risk patients were the use of valgancyclovir and the prescription of m-TORi as part of the immunosuppressive regimen. Although there is some previous experience suggesting some protective effect of anti-CMV drugs against the development of PTLD [21,22], the evidence supporting the use of (val-)ganciclovir in EBV-high-risk SOT is weak [10].

Our survey indicates that more than 85% of the centres apply some kind of EBV DNAemia monitoring in their patients (mostly lung and intestinal transplant recipients), and approximately one-third of participants report monitoring all SOT recipients. TID specialists appeared to be more restrictive regarding the use of EBV surveillance, applying this only to high-risk patients, as is currently recommended [10].

The information provided by transplant virologists points out the lack of standardization of EBV PCR assays. Whole blood samples were preferred in the majority of laboratories, but a great diversity was observed according to the viral sequence targeted by the QNAT assay, and considerable variability existed in the trigger point used to identify a patient at high risk that warrants pre-emptive or diagnostic strategies. On the other hand, a high variability regarding the time-points of EBV surveillance was observed. These basic issues, like which sample should be tested [23] or the timing of monitoring, have not been clearly determined [24–27] although measuring EBV loads in whole blood or white blood cells seems to be more sensitive [28]. Also, the identification of a clinical or diagnostic threshold remains obscure [24].

Given the lack of consensus on a fixed numeric threshold of EBV load for diagnosis or for pre-emptive intervention [24], some authors have suggested that the kinetics of EBV load may be the most informative parameter to define the risk of developing PTLD [25,29]. In that regard, the availability of a WHO International Standard for EBV for Nucleic Acid Techniques [14,26,30] should help to solve problems of inter-laboratory standardization [13].

Despite the limitations discussed above, almost 80% of transplant centres reported some kind of experience on the application of preventive measures directed by EBV DNAemia. Reduction of immunosuppression was the most frequently used (50% of the transplant programmes). The published experience on EBV pre-emptive strategies in the SOT setting invariably includes the reduction of immunosuppression, either as the sole strategy [31,32], or as a combination strategy with antiviral agents, immunoglobulins [33], or rituximab [34,35]; reduction of immunosuppression being the most clearly recommended measure [10].

Another frequently used pre-emptive measure was the switch from calcineurin inhibitors to m-TORi, which was reported in 30% of the centres. Although some case reports of encouraging responses have been communicated concerning patients with PTLD after a conversion from calcineurin inhibitors to mTORi [36], the current strength for recommending this pre-emptive strategy is weak [10,37].

The use of antivirals in patients with high-risk EBV DNAemia was reported in 22% of the institutions, valganciclovir being the drug most frequently prescribed. Unlike what happens in some SOT paediatric patients who are seronegative for EBV [38,39], there is no evidence that antiviral agents are helpful in EBV-seropositive SOT adult recipients with high EBV loads. However, some experts would consider the use of these antivirals as an adjunctive measure to the reduction of immunosuppression in selected patients [10].

Interestingly, pre-emptive therapy with rituximab was reported globally in 14.5% of the transplant programmes, and in more than 60% of paediatric transplant centres. Although some favourable experience of its use has been reported in SOT [34,35] the limited supporting evidence plus potentially severe adverse events had relegated this strategy to be a final step— to be considered in some patients with persistent and/or increasing EBV DNAemia in spite of reduction of immunosuppression [10].

An important first step to managing SOT recipients with high-risk EBV DNAemia is to reasonably rule out PTLD [10]. The results of the survey confirm that whole-body FDG-PET is frequently used for the workup of patients at risk for PTLD. More aggressive diagnostic techniques, such as biopsy of either the graft or the lymphatic nodes, are usually reserved for patients with clinical data suggestive of PTLD and only 4–6% of surveyed centres report its indication in patients with asymptomatic high-risk EBV DNAemia.

Apart from innate potential biases common to all online physician questionnaires, the major limitation of the present study was the low global response; the search for potentially active SOT programmes was based in web-based registries that could not be adequately updated and, therefore, the real number of active SOT programmes is presumably lower so that an under-estimation of the rate of survey response is probable.

Some important European countries, such as Germany, France and United Kingdom, were under-represented in the responders so the survey does not accurately represent the entirety of the centres performing SOT in northern Europe. On the other hand, it could constitute a significant bias because the centres that responded were the most sensitive to this issue and may not represent the usual practice in most other centres.

In summary, in view of the results of the present survey, pre-emptive management of EBV-related PTLD is an issue of concern for European physicians involved in SOT and the availability of EBV DNAemia assays for monitoring is currently a reality in the majority of SOT programmes. In spite of the lack of scientific supporting evidence, pre-emptive therapy is being performed in patients with high-risk EBV DNAemia in Europe, mostly through reduction of immunosuppression but also through the switch to m-TORi, the use of antiviral agents and even the administration of rituximab in some situations. More studies are needed focused on the accurate establishment of the population at risk for PTLD and the efficiency of EBV-monitoring-based pre-emptive management schedules in the SOT setting.

Contributions of the authors

RS-J participated in research design, analysis of results and writing of the paper. All other authors participated in research design and writing of the paper.

Transparency declaration

The authors of the present manuscript do not have a commercial or other association that might pose a conflict of interest (e.g. pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2015.02.002.

APPENDIX 1. ESGICH Survey on EBV-related PTLD Study Group (in alphabetical order)

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