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Reduction of Thymoglobuline from 7.5 mg/kg to 6 mg/kg in conditioning regimen extended time to the first cytomegalovirus detection after allogenic haematopoietic stem cell transplantation

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ABSTRACT

Introduction: The optimal dosage of anti-thymocyte globulin (ATG) may influence the outcome of patients after allogenic haematopoietic stem cell transplantation (HSCT). The aim of our study was to analyse human cytomegalovirus (CMV) infection data, incidence of graft-versus-host disease and other clinical endpoints comparing two patients' cohorts that were administered two different Thymoglobuline Genzyme doses as part of the HSCT conditioning regimen.
Materials and Methods: Total of 65 adult patients received ATG (7.5 mg/kg or 6 mg/kg) as a part of the fludarabine/busulfan/ATG conditioning regimen. CMV DNAemia was monitored after HSCT using quantitative real-time PCR and preemptive treatment was started for viral loads above 1000 cp/ml.
Results: The mild ATG dose reduction extended the time to the first CMV detection after transplantation (28 days for 7.5 mg/kg dose vs. 40 days for 6 mg/kg dose, p = 0.04). But it did not reduce the incidence or influence first anti-CMV treatment onset, the initial viral load, peak viral load in whole blood or the antiviral therapy parameters (all p ≥ 0.18). No impact of ATG dose reduction on incidence of graft-versus-host-disease, relapse of underlying disease or mortality within first year after transplantation (all p ≥ 0.32) were observed.
Conclusions: The reduced ATG dosages can allow lower toxicity of conditioning regimen while keeping the performance.

KEYWORDS

thymoglobuline – human cytomegalovirus – CMV – haematopoietic stem cell transplantation – GVHD

SOUHRN

Vejražková E., Hubáček P., Plíšková L., Košťál M., Zavřelová A., Štěpánová V., Žák P.: Snížení dávkování thymoglobulinu ze 7,5 mg/kg na 6 mg/kg v rámci přípravného transplantačního režimu prodloužilo dobu do první detekce lidského cytomegaloviru u pacientů po alogenní transplantaci krvetvorných buněk
Úvod: Stanovení optimálního dávkování antithymocytárního globulinu (ATG) použitého v rámci přípravného transplantačního režimu by mohlo zlepšit přežití u pacientů po alogenní transplantaci krvetvorných buněk (HSCT). V této práci byl hodnocen dopad snížení dávkování antithymocytárního globulinu (Thymoglobuline Genzyme) na cytomegalovirovou (CMV) infekci, incidenci reakce štěpu proti hostiteli (GVHD), celkové jednoroční přežití a další vybrané klinické parametry.
Materiál a metody: Do srovnání bylo zařazeno 65 pacientů se stejným transplantačním režimem (fludarabin/busulfan/thymoglobulin) s různým dávkováním thymoglobulinu: 7,5 vs. 6 mg/kg. CMV DNAémie byla pravidelně monitorována pomocí kvantitativní real-time PCR. Preemptivní antivirová terapie byla zahájena při virémii nad 1000 kopií CMV DNA v jednom mililitru periferní krve (cp/ml).
Výsledky: Snížení dávkování thymoglobulinu ze 7,5 mg/kg na 6 mg/kg prodloužilo dobu do první detekce CMV u pacientů po HCST (28 dní u vyššího dávkování vs. 40 dní u nižšího dávkování, p = 0,04). Změna dávkování neměla vliv na incidenci CMV, neovlivnila dobu do zahájení léčby ani celkovou délku podávání virostatik, nebyl rozdíl v úvodní virové náloži ani v maximální dosažené virémii (vše p ≥ 0,18). Nižší dávkování thymoglobulinu nevedlo k vyšší incidenci GVHD ani vyššímu riziku relapsu či mortalitě v prvním potransplantačním roce (vše p ≥ 0,32).
Závěr: Snížení dávkování ATG v rámci transplantačního přípravného režimu fludarabin/busulfan/thymoglobulin by mohlo přinést snížení toxicity léčby při zachování její účinnosti.

KLÍČOVÁ SLOVA

thymoglobulin – lidský cytomegalovirus – CMV – alogenní transplantace krvetvorných buněk – GVHD

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INTRODUCTION

Anti-thymocyte globulin (ATG) is used for T-cell depletion in vivo to prevent graft-versus-host-disease (GVHD) after allogenic haematopoietic stem cell transplantation (HSCT), but carries a risk of serious infection complication (including human cytomegalovirus (CMV) infection) or relapse of haematological malignancy [1, 2]. The optimal ATG dosage has not yet been established [1, 2] and its determination may influence the outcome of patients after HSCT.

The aim of our study was to analyse CMV infection data, GVHD, and other clinical endpoints in patients, comparing thymoglobuline doses of 7.5 mg/kg vs. 6 mg/kg as part of the conditioning regimen in adult HSCT recipients in our centre.

MATERIAL AND METHODS

Our prospective study included 65 patients after allogeneic HSCT transplanted due to haematological diseases at the Hradec Kralove University Hospital, Czech Republic between July 2012 and January 2015. The used conditioning regimen were ATG with fludarabine (30 mg/m^2 daily for 5 consecutive days prior to the graft infusion with a total dose of 150 mg/m^2 for myeloablative regimens; 6 consecutive days with total dose of 180 mg/m^2 for reduced intensity regimens) combined with busulfan (myeloablative regimens: 3.2 mg/kg daily for 4 consecutive days with a total dose of 12.8 mg/kg; reduced intensity regimens: 2–3 consecutive days a with total dose of 6.4–9.6 mg/kg). The ATG used was Thymoglobuline Genzyme (Cambridge, MA, USA, rabbit ATG) administered in days -3 to -1 as a total dose of 7.5 mg/kg and days -2 to -1 as a total dose of 6 mg/kg. There were no significant differences between patients' groups who were administered higher (n = 27 patients) and lower (n = 38 patients) ATG doses. For details see Table 1. Tacrolimus with mycophenolate mophetil was used as a posttransplant immunosuppression. The initial GVHD therapy was started using doses of methylprednisolone of 1–2 mg/kg, gradually reduced based on patients' clinical statuses. We used low dose methotrexate, cyclosporine A, sirolimus and photopheresis in cases of steroid-resistant GVHD. All patients received prophylactic treatment according to the institutional practice; trimethoprim-sulfamethoxazole as *Pneumocystis jirovecii* pneumonia prophylaxis, aciclovir prophylaxis and fluconazole. The length of prophylactic treatment was influenced by presence of GVHD or immunosuppressive therapy. Specific CMV prophylaxis (VGCV, valganciclovir) was used only in one patient after their heart transplantation, 296 days after HSCT. The follow-up was at least one year.

CMV DNAemia was determined by quantitative real-time PCR from whole blood as described previously [3]. The limit of detection was 100 copies of CMV DNA per millilitre (cp/ml, equivalent of 79.4 IU/ml) and the limit of quantification was 500 cp/ml of the assay. CMV DNAemia was monitored weekly until day 100 for patients with uncomplicated clinical statuses, surveillance then continued every 2–3 weeks.

CMV replication was considered if the viral load was above 100 cp/ml. Preemptive treatment using VGCV was started for viral loads above 1000 cp/ml. VGCV doses were 900 mg BID until viral load reduced to 50%. VGCV was then administered once a day for at least 2 weeks (maintenance therapy) until DNAemia was negative. Maintenance therapy was not initiated or was limited to one week if the initial viral load was lower than 10^4 cp/ml and DNAemia became negative during the initial therapy

Table 1. Patients' characteristics according to the ATG dosage

	ATG dosage: 7.5 mg/kg, n = 27	ATG dosage: 6 mg/kg, n = 38	*P* value of statistical significance
Age at time of HSCT (median, years)	56	60.5	0.42
Karnofsky Performance Status at time of HSCT (median)	80	80	0.31
Males/Females (%)	48/52	55/45	0.62
Donor age at time of HSCT (median, years)	29	29	0.89
The most common underlying disease (%)	AML (44.5)	AML (55.3)	0.45
Other underlying diseases (%)	ALL and CLL (both 18.5), MPD and NHL (both 7.4), MDS (3.7)	MDS (15.7), ALL (7.8), CLL, MPD, CMML and NHL (all 5.3)	each > 0.22
10/10 HLA – matched unrelated donor (%)	70	68	1.00
HLA – mismatched unrelated donor (9/10 or 8/10 match, %)	30	26	0.78
10/10 HLA – matched sibling donor (%)	0	5	0.50
34CD+ cell dose in HSCT graft (CD34$^+$ x 10^6/kg, median)	7	6.5	0.40
Myeloablative / reduced intensity conditioning regimen (%)	26/74	40/60	0.29
Achievement of complete remission before HSCT (%)	41	55	0.32
CMV seronegative donor/ seropositive recipient D-/R+ (%)	52	53	1.00
CMV seropositive donor and recipient D+/R+ (%)	30	29	1.00
CMV seropositive donor/ seronegative recipient D+/R- (%)	4	10	0.39
CMV seronegative donor and recipient D-/R-*(%)	14	8	0.43

*No primoinfection was recorded in this patient group – excluded from the statistics

Abbreviations: ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, ATG – anti-thymocyte globulin, CLL – chronic lymphocytic leukemia, CMML – chronic myelomonocytic leukemia, CMV – human cytomegalovirus, D – donor, HLA – human leukocyte antigen system, HSCT – hematopoietic stem cell transplantation, MDS – myelodysplastic syndrome, MPD – myeloproliferative disorders, NHL – non-Hodgkin lymphoma, R – recipient

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[3]. Ganciclovir (GCV, intravenous only) or foscarnet (FOS) treatment schema were used for CMV disease according to the NCCN Guidelines [4].
Categorical data was analysed using the Fisher exact test for 2 x 2 contingency table. Non-parametric Mann-Whitney test was used for comparing independent groups. P values ≤ 0.05 were considered statistically significant.
Study was reviewed and approved by University Hospital Hradec Kralove Ethics Committee.

RESULTS

The time to the first CMV DNA detection after HSCT was shorter in a cohort with higher ATG dosing (median of 28 vs. 40 days after HSCT, p = 0.043). No significant differences were found in CMV reactivation incidence after HSCT, the time of initiation or the length of antiviral therapy between these patients' groups (p = 0.18–0.87). No significant differences were also found in the initial viral loads, the peak viral loads, or the CMV disease incidence (p = 0.22–0.82).
The mild reduction of ATG had neither significant impact on full chimerism achievement nor influenced the time to the engraftment after HSCT (p = 0.25–0.99). The incidence of GVHD, graft failure, relapse of underlying disease or mortality within first year after HSCT did not differ between the groups (p = 0.32–0.76). See Table 2 and Table 3 for details.

Table 2. Incidence of CMV infection/reactivation and other CMV infection data during the first posttransplant year according to the ATG dosage

	ATG dosage: 7.5 mg/kg, n = 27	ATG dosage: 6 mg/kg, n = 38	P value of statistical significance
Incidence of CMV infection/reactivation after HSCT (%)	56	74	0.18
Time to 1st CMV reactivation (days after HSCT)	28	40	0.043
First anti-CMV treatment onset (days after HSCT)	40	42	0.20
The initial CMV DNA (cp/ml)	395	443	0.82
Peak viral load in whole blood (CMV DNA cp/ml)	4610	3175	0.42
Necessity of antiviral therapy (%)	93	86	0.64
Cumulative antiviral treatment (days)	40	41	0.87
CMV disease incidence* (%)	14.8	5.3	0.22

*Defined in Ljungman et al., 2002 [11]
Abbreviations: ATG – anti-thymocyte globulin, CMV – human cytomegalovirus, cp/ml – copies of CMV DNA per millilitre of whole blood, HSCT – hematopoietic stem cell transplantation

Table 3. Clinical data according to ATG dosage during the first posttransplant year

	ATG dosage: 7.5 mg/kg, n = 27	ATG dosage: 6 mg/kg, n = 38	*P* value of statistical significance
Complete chimerism achievement (%)	59	63	0.79
Achievement of complete chimerism (day after HSCT, median)	29	34	0.40
Time to engraftment*: leukocytes > 1 x 10^9/L (day after HSCT, median)	13.5*[2]	14.5*[3]	0.37
Time to engraftment*: neutrophiles > 0.5 x 10^9/L (day after HSCT, median)	16*[2]	16*[3]	0.99
Time to engraftment*: thrombocytes > 20 x 10^9L (day after HSCT, median)	16*[4]	16*[3]	0.25
Incidence of GVHD (%)	56	42	0.32
Necessity of systemic corticosteroid therapy for GVHD (%)	80	75	1.00
Graft failure (%)	4	0	0.42
Relapse occurrence (%)	26	21	0.76
All-cause mortality at day +100 after HSCT (%)	19	13	0.72
All-cause mortality at day +365 after HSCT (%)	44	34	0.44
Non-relapse morality at day +365 after HSCT (deaths from any cause without prior progression, %)	26	21	0.76

*According to the European Group for Blood and Marrow Transplantation classification [12]
*[2]One patient died before engraftment in the ATG 7.5 mg/kg group
*[3]One patient died before engraftment in the ATG 6 mg/kg group
*[4]Five patients died before engraftment in the ATG 7.5 mg/kg group
Abbreviations: ATG – anti-thymocyte globulin, GVHD – graft versus host disease, HSCT – hematopoietic stem cell transplantation

DISCUSSION

The time to the first CMV DNA detection after HSCT was significantly shorter in a cohort with higher ATG dosing, probably due to more potent T cell depletion. George et al. [5] proved an earlier onset of CMV reactivation in patients using ATG or alemtuzumab in reduced intensity conditioning regimens. Liu et al. [1] described that higher ATG dosage (10 vs. 6 mg/kg in haploidentical HSCT) negatively influenced recovery of particular lymphocytes (CD4+, CD4+CD45RA+, CD4+45RO+, CD4-CD8- and CD8+CD28+). ATG also impacts B cells, natural killer cells, macrophages and dendritic cells as well as HLA class 1 and HLA-DR [6, 7]. The flow cytometric analysis of lymphocyte subpopulation was not available at time of this work so detailed information of immune system recovery in HSCT recipients is missing.
We did not prove any difference in CMV incidence after HSCT using 7.5 vs. 6 mg ATG in conditioning regimens.

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This is in agreement with the large Beijing study [8]. There are two Ohio, USA studies [2, 9] with contradictory results for CMV infection. Both used different cut-offs for DNAemia significance levels as well as different post-HSCT monitoring periods; this can explain the contradictory results. The older study [9] which included all patients with any CMV detection (comparable to our work) showed a significant decrease in the risk of serious infections including CMV. Their patient cohorts were not fully comparable to ours as they were only including reduced intensity conditioning regimen recipients, a full third of patients' cohort was CMV seronegative for both patients and donors, most of the patients were transplanted in HLA 8/8 match, etc.

Our results showed no significant effect on engraftment or chimerism after the ATG doses reduction, matching other studies' results [8–10].

The mild reduction of ATG did not increase GVHD incidence and had no significant effect on mortality in our cohort, matching the published results [2, 8, 9]. A retrospective study by Ayuk et al. [6] showed a decreased 2-year transplant-related mortality with a lower dose of ATG-Fresenius (30 mg/kg) compared to a higher dose (60 mg/kg), mainly due to higher incidence of fatal infections in the ATG-60 group.

CONCLUSION

The reduction of ATG from 7.5 mg/kg to 6 mg/kg in conditioning regimen Fludarabine/Busulfan/ATG extended the time to the first CMV detection after HSCT but did not reduce incidence of CMV after HSCT. We did not observe any impact of ATG dose reduction on incidence of GVHD, relapse of underlying disease or mortality within first year after HSCT. We continue administering reduced ATG dosages to maintain lower toxicity while keeping the performance. Larger cohort of patients and longer follow up would be necessary to definitively confirm our results.

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