風疹に関して

表2　成人コントロール検体による至適条件の確認

number	cell number (×10^5)	medium		Ag		PHA	1×10^5個あたりのスポット数		備考
			mean		mean		none	Antigen	
C03	2.4	0 0 0	0	0 0 0	0	+ + +	0	0	ムンプスワクチン接種後
C04	2.4	0 2 0	0.66	28 33 23	28	+ + +	0.275	11.66666667	風疹ワクチン接種後
C06	1.8	0 0 0	0	0 0 1	0.33	+ + +	0	0.183333333	Non-responder
C08	2	0 0 0	0	0 1 0	0.33	+ + +	0	0.165	麻疹、風疹、ムンプスに対する免疫有り

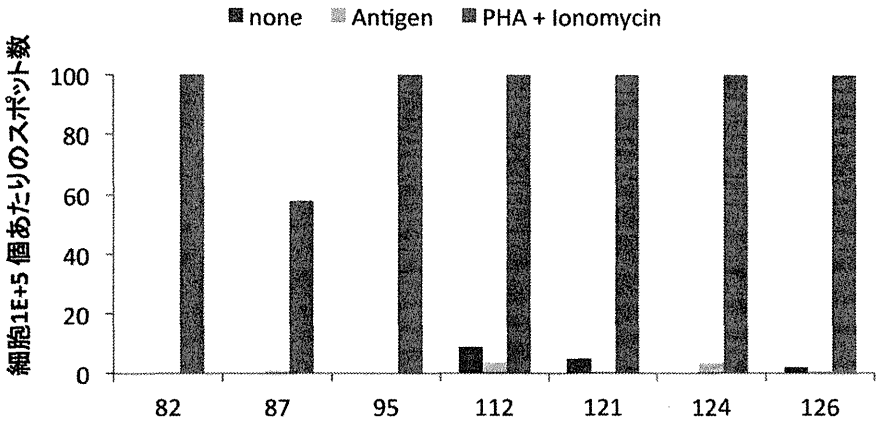
風疹に関して

表3

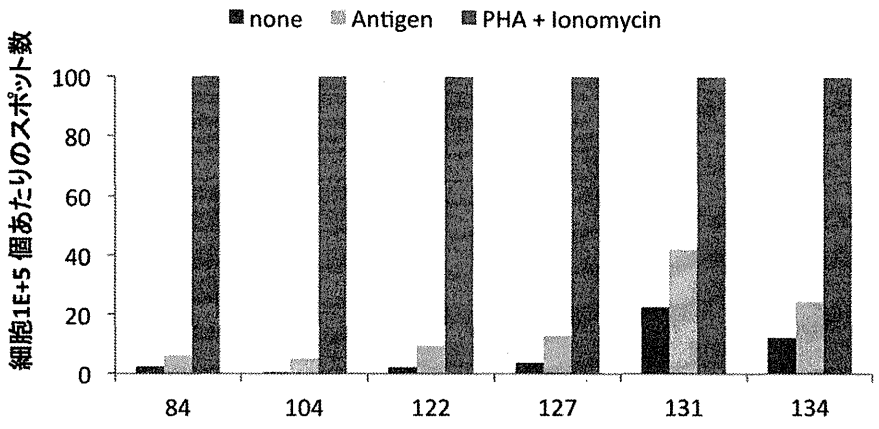
	検体数
陰性	132
陽性	6
測定不能	1
計	139

風疹に関して

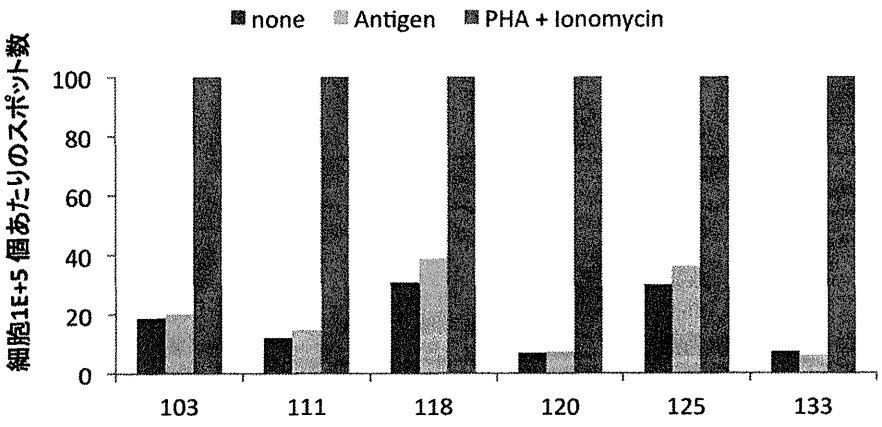
陰性検体(抜粋)



陽性検体



非特異反応検体



Ⅱ．研究成果の刊行に関する一覧表

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無し

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

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Ⅲ. 研究成果の刊行物・別刷

日本小児科学会雑誌　116巻5号　823～826（2012年）

総　説

基礎疾患をもつ小児に対する同時接種によるワクチン接種

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庄司　健介[1]　船木　孝則[1]　加藤　達夫[3]

要　旨

インフルエンザ菌b型（ヒブ）ワクチン，肺炎球菌ワクチンは，小児の重症細菌性感染症を予防するための重要なワクチンである．当センターでは，基礎疾患をもつ小児に対して，これらのワクチンを含む同時接種による予防接種を推奨し，2007年12月より2011年2月の間に計104名，のべ170回の同時接種を実施してきた．年齢の中央値は13か月(2か月～17歳)，1人当たりの接種時のワクチン接種数の中央値は3接種（範囲：2～7接種）であった．患者の基礎疾患としては，胆道閉鎖症などの消化器疾患，肝移植後，神経疾患，循環器疾患などが全体の約3/4を占めた．接種後28日までに報告された有害事象は1件，副反応は3件であった．基礎疾患をもつ小児は，ヒブ，肺炎球菌などの細菌感染症に感染すると重症化する危険性が高い．したがって，これらの小児をワクチンで予防できる疾患から守るためには，混合ワクチンの少ない現在の日本においては，同時接種による効率のよい，かつ早期の接種が重要である．

キーワード：小児，予防接種，同時接種，安全性，基礎疾患

はじめに

基礎疾患を持つ乳幼児は，生直後からその時間の大半を診断，治療などに費やすことが多く，予防接種可能な時期に限界がある．一方で，心臓疾患や，薬剤による免疫抑制状態におかれた基礎疾患のある乳幼児が，インフルエンザ菌b型(ヒブ)，肺炎球菌などの細菌感染症に罹患すると，一般健常児に比べ，重症化し，予後と死亡率に大きな影響を与える可能性がある．

WHOが世界の乳幼児に接種を推奨しているワクチンの中で，ヒブワクチン，結合型肺炎球菌ワクチンは，国内でそれぞれ2008年12月，2010年2月に販売された．海外においては，これらのワクチンは既に普及しており，ヒブ感染症[1]，肺炎球菌感染症[2]は減少，その疾患の疫学を大きく変えるまでに至った．一方で，これらのワクチンは，乳幼児期早期に接種を完了することで，その最大限の効果をもたらすことが出来る．早期接種するためには，他の必要なワクチンとの同時接種が必要である[3]．しかしながら，本邦においては，予防接種は，原則1回に1ワクチン，ただし，あらかじめ混合されていない2種以上のワクチンについて，医師が必要と認めた場合には，同時に接種を行うことができるとされている[4]．国内において健常児におけるヒブワクチンを含むワクチンの同時接種の安全性はデータが存在するが[5]，基礎疾患を持つ乳幼児に対して，両ワクチンを含めた同時接種の際の安全性に関しての情報は存在しない．

当センターでは，特にヒブワクチン，肺炎球菌ワクチン販売後，基礎疾患を持つ小児に対して，積極的に同時接種による効率的な予防接種を推奨してきた．

方　法

2007年12月より2011年2月までに国立成育医療研究センターにおいて，同時接種を実施した基礎疾患をもつ小児，計104名の接種年齢，接種ワクチン，接種後28日までの有害事象，副反応などの以上情報を電子カルテをもとに抽出した．実際の接種は，当センター外来看護師によって，両上腕の外伸側下1/3，両上腕三角筋上部に接種が実施され，接種本数が4本以上の場合は，担当の医師が実際に接種を行った．

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結　果

1）同時接種患者の背景

同時接種は，計104名に対して，のべ170回の接種が実施された．性別は，男性42名（40%），女性62名（60%）であり，年齢の中央値は13か月（2か月～17歳），1人当たりの1回接種の中央値は3接種（範囲：2～7接種）であった．患者の基礎疾患は，胆道閉鎖症などの消化器疾患，肝移植後，神経疾患，循環器疾患などが全体の約3/4を占めた（図1）．

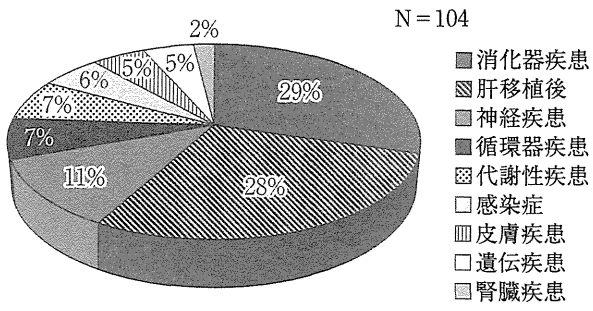

図1　全患者の基礎疾患の内訳

2）接種の状況（表1）

i）三種混合（DPT）ワクチン，ヒブワクチン，肺炎球菌ワクチンの同時接種

3つのワクチンの同時接種は，肺炎球菌ワクチン発売後の2010年2月から実施され，計36接種(29症例)に実施された．年齢の中央値は5か月（範囲：3～40か月），性別は，男性16名(55%)，女性13名(45%)であり，更にその中の5接種においては，他のワクチンとの同時接種を実施した．その内訳は，上記3つのワクチンに加えて，B型肝炎ワクチン（2接種），BCGワクチン(1接種)，インフルエンザワクチン(1接種)，MRワクチン＋水痘ワクチン＋B型肝炎ワクチン（1接種）であった．

ii）ヒブワクチンを含む同時接種（31接種，29人）

ヒブワクチンを含む同時接種(ただし，DPTワクチン，ヒブワクチン，肺炎球菌ワクチンの3つのワクチンの同時接種を除く)は，計18接種(17症例)に実施され，2008年12月のヒブワクチン発売後から開始された．年齢の中央値は24か月(範囲：2～43か月)，性別：男性9名（31%），女性20名（69%）であった．ヒブワクチンとDPTワクチンの同時接種は，5接種，4名に実施され，その中の3接種では，更に上記2つのワクチンに加えて，B型肝炎（1接種），B型肝炎＋インフルエンザ(2接種)の同時接種が実施された．一方で，ヒブワクチンと肺炎球菌の同時接種は，18接種(17人）に行われ，更なるワクチンの同時接種を11接種で行った．その内訳は，上記2つのワクチンに加えてMRワクチン(3接種)，インフルエンザワクチン(3接種)，B型肝炎ワクチン(3接種)，インフルエンザワクチン＋B型肝炎ワクチン（1接種），インフルエンザワクチン＋ムンプスワクチン＋水痘ワクチン（1接種）であった．ヒブワクチンとその他のワクチンとの同時接種は8接種（8人）に行われた．

iii）肺炎球菌ワクチンを含む同時接種34接種（30人）

肺炎球菌ワクチンを含む同時接種（ただし，DPTワクチン，ヒブワクチン，肺炎球菌ワクチンの3つのワクチンの同時接種，並びに，ヒブワクチンと肺炎球菌ワクチンの同時接種を除く)は，男性10名(33%)，女性20名（64%）に実施され，年齢の中央値は，31か月(2～94か月)であった．肺炎球菌ワクチンとDPTワクチンの同時接種は，15接種（13人）に実施され，更なるワクチンの同時接種を6接種で行った．その内訳は，上記2ワクチンに加えて，B型肝炎ワクチン(3接種)，MRワクチン(2接種)，MRワクチン＋ムンプスワクチン＋水痘ワクチン(1接種)であった．また，肺炎球菌とその他のワクチンとの同時接種は19接種(17人）に実施された．

3）ワクチン接種後の有害事象，副反応

i）有害事象

報告された有害事象は1件（1/170, 0.5%）で，2歳3か月女児，肝移植後で，ヒブ，肺炎球菌，B型肝炎ワクチンを接種，接種後4時間後に頻回の嘔吐があり，救急室を受診したが，経過観察で改善した．ワクチン接種との直接の因果関係はないものと考えられた．

ii）副反応

報告されたワクチン接種後の副反応は，計3件（3/170, 1.7%）であった．それぞれの具体例を記載する．

症例1）4歳9か月女児，壊血病（栄養不良）を持つ児で，MR，水痘，ムンプスワクチンを同時接種後25日目に水痘を発症した．分離されたウイルスは，ワクチン株であることが判明し，症状は，自然経過で改善した．ワクチン株のウイルスが同定されたことにより，ワクチンとの因果関係ありと判断された．

症例2）1歳1か月女児，気管支喘息，アトピー性皮膚炎を持つ児で，MR，ヒブ，肺炎球菌ワクチン接種翌日に局所の発赤があったが，自然に軽快した．

症例3）9か月女児，胆道閉鎖症術後，肝移植前の接種で，MR，水痘，ムンプス，B型肝炎，日本脳炎，ヒブ，BCGワクチンの計7つのワクチン接種6時間後に発熱，2日後に解熱した．因果関係は明らかではなかったが，他の発熱の誘因，症状が同定されなかった．

表1　ヒブワクチン，肺炎球菌ワクチンを含んだ同時接種後28日までの副反応と有害事象

同時接種に含まれたワクチン			接種総数	接種患者数	副反応	有害事象
DPT	ヒブ	肺炎球菌				
○	○	○	36（49%）	29（46%）	0	0
○	○		5（7%）	4（6%）	0	0
○		○	15（20%）	13（21%）	0	0
	○	○	18（24%）	17（27%）	2例（発熱，局所の発赤）	1（嘔吐）
合計			74（100%）	63（100%）	2	1

考　察

今回，我々は，国立成育医療研究センターにおいて，基礎疾患をもつ小児に対するヒブワクチン，肺炎球菌ワクチンを含む同時接種を，計104名，のべ170回の接種を実施し，安全に実施できることを確認した．

同時接種については，海外では，既に幅広く実施されている医療行為であり[6][7]，複数のワクチン（生ワクチンを含む）を同時接種して，それぞれのワクチンに対する有効性について，お互いのワクチンによる干渉はないこと，複数のワクチン（生ワクチンを含む）を同時に接種して，それぞれのワクチンの有害事象，副反応の頻度が上がることはないことが確認されている[8]．一方で，同時接種において，接種できるワクチン(生ワクチンを含む)の本数に原則制限はないことも知られている[8]．同時接種の利点としては，特に基礎疾患のある児において，各ワクチンの接種率が向上し，ワクチンで予防される疾患から早期に守られること，保護者の経済的，時間的負担が減少すること，更には，医療者の時間的負担が減少することがあげられる．一方で，その短所としては，一回に多くの接種を実施するため，最終的な痛みの回数は同じであるものの，被接種者の一時的な複数の疼痛があげられる．

基礎疾患を持つ小児に対する予防接種は，予防接種を実施できる時期が限られていることから，出来るだけ効率よく予防接種を進めなくてはいけない．米国小児科学会は，基礎疾患を持つ児への予防接種は，特に禁忌がない限り，健常児と同様に接種されるべきであるとしている[9]．日本小児科学会は，同時接種は，予防接種を効率的に行うために重要かつ必要な医療行為であるという考え方を2011年1月に発表した[10]．また，2011年5月には，同時接種を基本とした予防接種スケジュールを発表し，同時接種によって，日本の子どもたちがより早期からワクチンで予防できる病気から守られるように提言をしている[10]．この考え方は，健康な小児のみならず，特に基礎疾患を持つ小児において，重要な概念であると考える．

2011年3月に，ヒブ，肺炎球菌ワクチンを含む同時接種1～7日後に7名の乳幼児の死亡例が報告され，2011年3月4日から3月31日まで，2つのワクチンの一時接種見合わせが行われた[11]．その間に，計3回の専門家による委員会が開催され，2つのワクチンと死亡例との間には，直接の因果関係がないこと，また，同時接種の安全性にも問題がないことが確認された．しかしながら，実際の医療現場においては，この一時見合わせのインパクトは極めて大きかったことは事実である．

一方で，乳児期早期のワクチンスケジュールはより過密になってきている．前述の一時見合わせの後にはヒブ，肺炎球ワクチンの添付文書には，基礎疾患のある小児には単回接種も考慮することとの一文が加わった．2011年11月には1価のロタウイルスワクチンが導入され，2012年には，5価のロタウイルスワクチン，更には，不活化ポリオワクチン，並びに三種混合ワクチン＋不活化ポリオワクチンの混合ワクチンも国内に導入される予定である．継続的にワクチンによる有害事象，副反応のモニタリングを行わないと前回と同様の事象が起った場合，予防接種の差し止めが起こる可能性がある．また，疾患そのもののサーベイランス，ワクチンによる有害事象，副反応のサーベイランスに加えて，この様な差し止めの是非や，新しいワクチンの導入．既に導入されたワクチンの効果，安全性の検証を行う米国ACIP（Advisory Committee on Immunization Practices）に代表されるような国のワクチン諮問機関（NITAG：National Immunization Technical Advisory Group）[12]の早期設立が望まれる[13]．

今回の後方視的研究の限界は，患者の有害事象，副反応を電子カルテから抽出したことによって，患者に有害事象，副反応が発生した場合でも，それが両親，本人の注意を引かない場合，あるいは軽症の場合，報告されていない可能性がある．したがって，有害事象，副反応の頻度が低く報告されている可能性がある．また，今回検討した104例，170接種では，頻度の少ない

有害事象，副反応の現状をとらえることは不可能であり，上述したような，有害事象，副反応の継続的サーベイランスが必要である．

日本において，同時接種という医療行為が普及するためには，その医療行為に対する啓発活動がまず重要である．また，予防接種を適切な時期に，いかに効率的に接種するかを啓発する活動も，重要な課題である．基礎疾患のある小児を含めて，日本の子どもたちがワクチンで予防できる疾患から守られるためには，混合ワクチンの少ない現在の日本においては，ワクチンを乳幼児早期に確実に，適切な時期に接種しなくてはならず，そのためには同時接種は必要な医療行為であり，その理解と普及が望まれる．

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Safety of Simultaneous Vaccination in Children with Underlining Diseases

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Vaccines for *Haemophilus influenzae* type b and *Streptococcus pneumoniae* for children are important to prevent invasive bacterial infections by these organisms. At the Center for Child Health and Development, Tokyo, Japan, we have recommended providing simultaneous vaccination for children with underlying diseases. We performed 104 children, in a total of 170 opportunities for children with underlying diseases between December, 2007 and February, 2011. The median age was 13 months (range: 2 months—17 years), the median numbers of vaccination per visit was 3 (range: 2—7). Approximately 75% of baseline diseases are gastrointestinal diseases including biliary atresia, status post liver transplantation, neurologic diseases, and cardiac diseases. Only one adverse event and three side effects were observed within 28 days after the simultaneous vaccination. Simultaneous vaccination is a common medical practice around the world. The risks for invasive infections by *Haemophilus influenzae* type b and *Streptococcus pneumoniae* are high in children with underlying diseases. To prevent the infections for high risk individuals, it is necessary to perform simultaneous vaccination to provide effective and appropriate protection against vaccine preventable diseases.

A Universal Preemptive Therapy for Cytomegalovirus Infections in Children After Live-Donor Liver Transplantation

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Background. Cytomegalovirus (CMV) infection remains the most common and critical viral infection that occurs after liver transplantation (LT). The current set of guidelines recommends prophylaxis over a preemptive therapy for pediatric LT; however, the data regarding the optimal approach after LT in children are limited.
Methods. We conducted a universal preemptive therapy for CMV infection in 113 children (median: 16 months) after live-donor LT at the largest pediatric LT center in Japan between November 2005 and August 2009. CMV-pp65 antigenemia was monitored weekly regardless of the subjects' CMV serostatus after LT, and ganciclovir therapy was initiated when CMV-pp65 antigenemia was positive.
Results. The overall success rate of LT was 91.7%. CMV-pp65 antigenemia became positive in 37 (33%) recipients, and the positivity with their CMV serostatus was as follows: donor (D)+/recipient (R)−: 62%, D+/R+: 36%, D−/R+: 11%, and D−/R−: 8%. Among the D+/R− (n=29) and D+/R+ (n=44) recipients, 38% (n=11) and 64% (n=28) recipients were able to avoid the use of ganciclovir, respectively. Human CMV disease was documented in six (5%) recipients, and they were successfully treated with ganciclovir without any sequelae.
Conclusions. A universal preemptive therapy for CMV infection after live-donor LT was successful for reducing the use of antiviral agents and for controlling CMV infection and disease in children.

Keywords: Cytomegalovirus, Liver transplantation, Children, Preemptive therapy, Ganciclovir.

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Cytomegalovirus (CMV) remains the most common infection that occurs after liver transplantation (LT) in children (*1*). Human CMV (HCMV) can cause various diseases affecting different organs, and it may contribute to rejection (*2*), fungal infections (*3*), and the risk for the Epstein-Barr virus-related posttransplant lymphoproliferative disorders (*4*). However, recent advances in preventive strategies for CMV have led to a significant decrease in the incidence of HCMV disease (*5*).

There have been two major approaches to control CMV infection after LT: universal prophylaxis and preemptive therapy. Universal prophylaxis provides antiviral therapy for subjects with a high risk of developing HCMV disease, such as seronegative recipients receiving seropositive grafts, for certain period of time (e.g., 2–14 weeks) (*6, 7*). In contrast, a preemptive approach provides antiviral therapy for subjects who have positive results for routine monitoring of CMV antigenemia or polymerase chain reaction (PCR). Previous studies have shown the effectiveness of preemptive therapy for solid organ transplant recipients, primarily in adults (*7–10*), but little data are available for children after LT (*11, 12*). Furthermore, no study has evaluated a preemptive therapy for children with the highest risk of developing a CMV infection (e.g., donor (D)+/recipient (R)−). Children are at a higher risk of developing a CMV infection because pediatric organ recipients have a higher chance of being seronegative for CMV compared with adult recipients. Thus, more information is necessary to elucidate the importance of preemptive therapy to prevent and treat HCMV infections and disease.

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TABLE 1. The clinical outcome in recipients based on the donor's and recipient's cytomegalovirus serologic status

D/R CMV serologic status						
Donor	Recipient	N (%)	Age median month (IQR)	Number of recipients with CMV-pp65 Ag positive (%)	Number of recipients with CMV diseases (%)	Number of recipients with acute rejection (%)
+	−	35 (31%)	19 (9–52)	22 (63%)	4 (11%)	22 (42%)
+	+	53 (47%)	8 (14–103)	20 (38%)	1 (2%)	10 (29%)
−	+	9 (8%)	8 (5–10)	1 (11%)	0 (0%)	2 (9%)
−	−	16 (14%)	30 (10–60)	1 (6%)	1 (6%)	5 (31%)
Total		113 (100%)	16 (8–66)	44 (39%)	6 (5%)	39 (5%)

D, donor; R, recipient; CMV, cytomegalovirus; Ag, antigen; IQR, interquartile range.

The pediatric LT program at the National Center for Child Health and Development, Tokyo, is the largest pediatric LT program in Japan. The program has performed a universal preemptive therapy monitoring CMV-pp65 antigenemia weekly for CMV prevention for all recipients regardless of their CMV status since November 2005. We herein report the impact of preemptive therapy on the incidence and clinical outcome of HCMV infection and disease in children after live-donor LT.

RESULTS

Patient Characteristics

We performed 113 live-donor LT at our institution between November 2005 and December 2009, and the clinical course and outcome of these patients were monitored for at least 6 months after LT. The baseline information of the 113 children who received live-donor LT is summarized in Table 1. The median age of the recipients was 16 months (range: 1 month–21 years). The most common indication for live-donor LT was biliary atresia (n=49, 43%), followed by metabolic diseases (n=26, 23%), acute liver failure (n=20, 18%), liver cirrhosis (n=10, 9%), vascular abnormalities (n=5, 4%), and hepatic tumors (n=3, 3%). Eleven patients (9.7%) died after live-donor LT during the first year after LT, and the reasons for their deaths were not directly related to HCMV disease.

CMV Serostatus and CMV-pp65 Antigenemia Positivity

The CMV serostatus of the donors and recipients is presented in Table 1. The median time to become positive for CMV-pp65 antigenemia was 33 days postoperatively (interquartile range [IQR]: 17.5 days, range: −8 to 115 days). Of note, two cases were CMV-pp65 antigenemia positive before LT, and both patients were treated with ganciclovir (GCV) pre and postoperatively. The median CMV-positive cells were 3 of 50,000 cells (IQR: 8/50,000 cells, range: 1–201/50,000 cells). The highest CMV-pp65 antigenemia positivity was observed in 63% (22/35) of patients in the D+/R− group, followed by 38% (20/53) in the D+/R+ group. In the D−/R+ and D−/R− groups, only one recipient in each group was positive for CMV-pp65 antigenemia (Table 1). As expected, the proportion of recipients who remained negative for CMV-pp65 antigenemia for the 6 months after LT was significantly affected by the CMV serostatus of the donors and recipients (Figure 1).

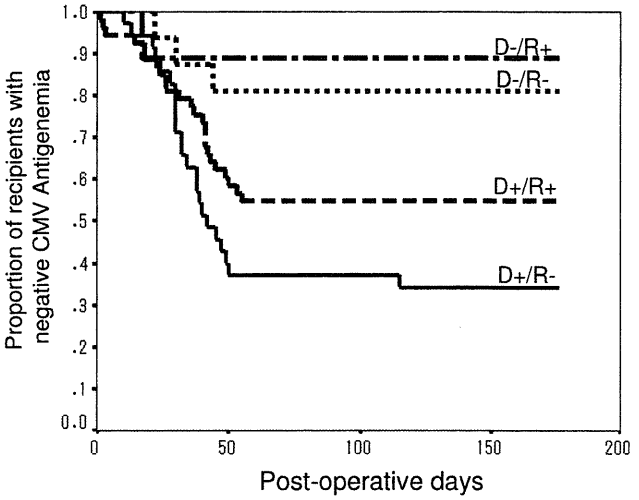

FIGURE 1. A proportion of patients were negative for cytomegalovirus antigenemia based on cytomegalovirus serostatus for the first 180 days after live-donor liver transplantation. D, donor; R, recipient.

Treatment for CMV-pp65 Antigenemia

During the observational period, 44 (39%) recipients had positive tests for CMV-pp65 antigenemia. Among the 44 patients, 38 (86%) patients received intravenous (IV) GCV as an initial therapy. The median duration of GCV therapy was 14 days (range: 6–24 days). IV foscarnet was given to four (9%) recipients when infection by GCV-resistant strains was suspected after GCV induction therapy; however, no GCV resistant strain was identified by the sequence analyses. GCV was switched to valganciclovir for three (8%) recipients after successful GCV induction therapy when valganciclovir became available in 2009. Neutropenia (absolute neutrophile counts $<500/\mu L$) was observed in three (7%) recipients, but their neutropenia resolved after discontinuation of therapy. Retreatment with GCV was required for four (9%) recipients. Of note, six (14%) recipients who had positive CMV-pp65 antigenemia after LT did not require antiviral treatment because repeated CMV-pp65 antigenemia in the same week became indeterminate or negative when the patients' immunosuppressive therapy was decreased. Four patients were treated with IV immunoglobulin to control HCMV disease.

Treatment of Recipients at High Risks for CMV

Among the highest risk group for CMV (D+/R−), 20 of 35 (57%) recipients required GCV due to positivity for CMV-pp65 antigenemia, with a median duration of 14 days (IQR: 3.8 days). Two (6%) patients did not receive GCV because the repeated CMV-pp65 antigenemia evaluation in the same week dropped to within an indeterminate range. In contrast, 15 of 35 (43%) recipients were able to avoid the use of GCV. Similarly, among the patients in the D+/R+ group, 16 of 53 (30%) recipients required GCV therapy for positive CMV-pp65 antigenemia, with a median duration of 14 days (IQR: 3.0 days). Four patients (8%) did not receive GCV because the repeated CMV-pp65 antigenemia evaluation in the same week was negative or within an indeterminate range. In contrast, 37 of 53 (70%) recipients were able to avoid the use of GCV that they would have received if they were on universal prophylaxis.

Comparison Between Recipients Positive for CMV-pp65 Antigenemia and Those Negative for CMV-pp65 Antigenemia

We compared the baseline characteristics of recipients who were positive for CMV-pp65 antigenemia and those who were negative for CMV-pp65 antigenemia (Table 2). No differences were found between the two groups in age or sex. Recipients who received LT for acute liver failure tended to have a higher rate of positive CMV-pp65 antigenemia (70%, 14/20), in contrast, recipients with cholestatic liver diseases tended to have a lower rate of positive CMV-pp65 antigenemia (20%, 10/49). Among patients with positive CMV-pp65 antigenemia, 95% of recipients (42/44) were in either D+/R− or D+/R+ groups.

TABLE 2. The baseline characteristics of recipients determined by CMV-pp65 antigenemia status

Variables	CMV-pp65antigenemia negative (N = 69)	CMV-pp65 antigenemia positive (N = 44)	*P*
Median age, mo (IQR)	16 (8–81)	17 (7–56)	0.48
Gender, male, N (%)	28 (41)	24 (55)	0.15
Baseline diseases, N (%)			
Biliary atresia	39 (57)	10 (23)	<0.001
Metabolic diseases	14 (20)	12 (27)	0.39
Acute liver failure	6 (9)	14 (32)	0.002
Cirrhosis	5 (7)	5 (11)	0.45
Tumor	3 (4)	0 (0)	0.28
Vascular	2 (3)	3 (7)	0.38
CMV serologic status, N (%)			
D+/R−	13 (19)	22 (50)	<0.001
D+/R+	33 (48)	20 (45)	0.80
D−/R+	8 (12)	1 (2)	0.09
D−/R−	15 (22)	1 (2)	0.004

D, donor; R, recipient; CMV, cytomegalovirus.

Clinical Outcome

All patients were successfully treated with GCV for 2 to 4 weeks, and their symptoms and signs resolved and CMV-pp65 antigenemia became negative when the treatment was completed. Overall, only 6 of 113 (5%) recipients developed HCMV disease including CMV syndrome (n=3), hepatitis (n=1), enterocolitis (n=1), and pneumonitis (n=1). No complications or sequelae were noted in these four recipients with HCMV disease. Seven (6%) recipients were retreated with GCV when CMV-pp65 antigenemia became positive after the completion of the initial GCV therapy.

Acute rejection was observed in 39 (35%) recipients after LT. The median duration from LT to the time when the diagnosis of acute rejection was made was 12 days (range: 6–50 days) postoperatively. No significant difference was found between the time for acute rejection and the CMV serostatus; 11.5 days (range: 7–50 days) in the D+/R− group, 12 days (range: 6–37 days) in the D+/R+ group, 22.5 days (range: 13–32 days) in the D−/R+ group, and 16 days (range: 8–30 days) in the D−/R− group (P=0.39). In addition, no association was found between the incidence of acute rejection and CMV-pp65 antigenemia; among 39 patients positive for CMV-pp65 antigenemia, 17 patients (44%) developed acute rejection, whereas 27 of 74 (36%) of the patients negative for CMV-pp65 antigenemia after LT developed acute rejection (P=0.46). Only two patients (both were D+/R+) developed acute rejection subsequent to positive CMV-pp65 antigenemia.

Overall, 11 of 113 (9.7%) patients died after the live-donor LT due to sepsis (n=5, 45%), graft failure (n=5, 45%), and tumor recurrence (n=1, 10%). Among children with graft failure, no recipients had positive CMV-pp65 antigenemia after LT. Therefore, no recipients died due to HCMV infection or disease.

DISCUSSION

This is the first study to demonstrate that a universal preemptive therapy was effective to prevent the development of HCMV disease in children after LT, notably in children with the highest risk for HCMV disease (e.g., D+/R−). This universal approach was successful to target therapy to the recipients who developed early evidence of CMV reactivation and thereby decrease drug costs and toxicity for patients who do not need the treatments.

Reviewing the current guidelines proposed by the Transplantation Society International CMV Consensus Group (*13*), the administration of GCV for 12 weeks is the recommended regimen for any D+/R− transplants and R+ liver transplants, and no preemptive approach is recommended. The only recommendation by some experts for a preemptive approach is 2 to 4 weeks of prophylaxis, followed by preemptive therapy as an alternative therapy (*14*). No current recommendation is available with respect to a universal preemptive approach for pediatric LT recipients (*15*).

The major advantage of preemptive therapy is to limit the periods of antiviral treatment in children in whom antivirals are necessary for preventing HCMV disease. Gerna et al. (*12*) demonstrated equal efficacy of universal prophylaxis and preemptive therapy in 21 pediatric liver transplant recipients for preventing HCMV diseases, although the duration of

antiviral therapy was significantly shorter in the preemptive group compared with the universal prophylaxis group (18 vs. 30 days). Madan et al. (*11*) demonstrated the usefulness of a combination of a short course of antiviral prophylaxis (≥14 days) for high-risk patients (D+/R−) and preemptive monthly CMV PCR monitoring in children after LT. With this approach, 12 subjects (9.8%) developed HCMV disease, and there were no mortalities secondary to CMV. This approach spared a total of 39% of the patients from the use of antiviral medications beyond their initial postoperative prophylactic period. In this study, we were able to avoid the use of GCV in 13 of 35 (37%) recipients in the D+/R− group and 37 of 53 (70%) recipients in the D+/R+ group. In addition, the long-term use of GCV or valganciclovir for the treatment or prevention of CMV in children is a concern. The major toxicities in patients receiving GCV are bone marrow suppression and renal toxicity (*16*). Additionally, animal studies have suggested that GCV may cause gonadal toxicity (*17*) or carcinogenicity (*18*). Finally, the long-term use of antivirals is costly and may increase the chance of developing GCV-resistant virus strains after prolonged exposure (*19*). The major advantages of universal prophylaxis are that there is no need for virologic monitoring for CMV infection after LT. Regular monitoring of CMV-pp65 antigenemia or CMV-DNA PCR is costly and labor intensive; however, a few studies suggested that the cost of the preemptive approach is actually lower than the cost of universal prophylaxis in adults (*20*, *21*). In preemptive approach, a delayed response to the test results may delay the treatment for patients, thus resulting in increased diseases and higher costs of treatment.

Given the challenge of characterizing the recipient serostatus in those less than 18 months of age, any CMV seropositive recipient who is less than 18 months of age should be considered to be seronegative, as maternal antibodies may account for this finding. Therefore, CMV urine culture or nucleic acid amplification testing for all seropositive recipients is recommended (*13*). However, negative tests do not exclude the exposure to CMV, because negative tests may result from the intermittent shedding of the virus. In this study, not all recipients less than 18 months of age with positive CMV antibodies were tested for CMV-pp65 antigenemia at baseline; therefore, we analyzed the data solely using their CMV serostatus. In this study, 28 (53%) patients among the 53 D+/R+ patients were less than 18 months of age, and we assumed that the majority of patients were seronegative (D+/R−). This assumption favors the use of a preemptive approach because it allows for the inclusion of more recipients with the highest risk (D+/R−) of developing CMV reactivation.

Oral valganciclovir was used for three patients after successful GCV induction therapy. Valganciclovir has excellent oral bioavailability, resulting in systemic drug levels that are comparable with IV GCV in patients after LT (*22*). The oral bioavailability of valganciclovir in neonates and infants has also been confirmed by other studies (*23*). However, the current guideline does not recommend preemptive therapy using oral valganciclovir for LT recipients (*15*) due to the absence of adequate pharmacokinetics and efficacy data. In addition, one study indicated that the incidence of HCMV disease was higher in the patients receiving valganciclovir compared with GCV in the subgroup analysis of CMV D+/R− solid organ transplant recipients (*24*). Because CMV infection usually becomes apparent approximately 3 weeks after LT, the majority of recipients can tolerate oral valganciclovir by that time, and the option of using oral medication is practical and reasonable. Further studies to compare these two medications are needed to demonstrate the effectiveness of valganciclovir in children after LT.

There are a few limitations to this study. First, because of the study design, we had a limited number of recipients after LT and were unable to directly compare universal prophylaxis and a universal preemptive therapy for HCMV disease in children. Second, we have used the cutoff for a positive CMV-pp65 antigenemia as ≥5/50,000 cells, but this is not the standardized value. Further studies are necessary to determine the optimal cutoff value of CMV-pp65 antigenemia and to compare it with the results of CMV-DNA PCR. Third, this study included only subjects who received live-donor LT, which requires less immunosuppression compared with cadaveric LT; therefore, caution is required when this approach is used for the patients who receive a cadaver liver for the LT. Finally, judicious use of IV sodium was not performed in four recipients. Sodium was initiated when CMV-pp65 antigenemia persistently increased after more than 2-week course of GCV induction therapy; however, the event of delayed antigenemia decrease after appropriate treatment with GCV without GCV resistant virus has been clearly documented (*25*, *26*).

In conclusion, a universal preemptive therapy in children after live-donor LT was safe and successful at the largest pediatric LT center in Japan. A further prospective study is necessary to identify the best approach to preventing and treating HCMV disease in children after LT.

MATERIALS AND METHODS

Subjects

The study subjects comprised 113 children who received live-donor LT at the National Center for Child Health and Development in Tokyo, the largest pediatric LT center in Japan, between November 2005 and December 2009. This study was a retrospective evaluation of the standard protocol, which has been performed at our institution. The following information was extracted from the medical record database; age, gender, and HCMV serostatus of the donors and recipients, baseline diseases, reasons for LT, the first postoperative date positive for HCMV-pp65 antigenemia, antiviral treatment and its duration, HCMV disease, clinical outcome, and mortality.

Monitoring of CMV-pp65 Antigenemia

CMV-pp65 antigenemia was measured by a direct immunoperoxidase technique using a horseradish peroxydase-conjugated F(ab')2 fragment of human monoclonal (humab C7), designated horseradish peroxydase-C7 (*27*). The measurements were performed weekly for the first 3 months postoperatively, while the recipients were hospitalized, then monthly in an outpatient setting until 6 months after LT. We determined that the presence of more than 5 CMV antigen-positive cells/50,000 cells indicated that the patient was positive, and 1 to 5 positive cells/50,000 cells were considered to be an indeterminate result. Once the result was positive, a repeated CMV-pp65 antigenemia was performed within the same week in some of the patients, particularly when the value was close to the cutoff. The test results were returned to the primary care physicians less than 48 hr after the sample was taken and then were used to select the patients' treatment strategies.

Immunosuppressive and Antiviral Therapies

After LT, standard immunosuppression consisted of corticosteroids and tacrolimus. The corticosteroid was started intraoperatively (10 mg/kg/dose) and continued with tapering for the first 3 months after LT (1.0 mg/kg/day IV [days 1–3], 0.5 mg/kg/day IV [days 4–6], 0.3 mg/kg/day IV [day 7], 0.3 mg/kg/day orally (PO) [days 8–28], 0.1 mg/kg/day PO [days 29–90]). Tacrolimus was also started 1 day before surgery, and the dose was adjusted to maintain a trough level of 10 to 15 mg/L for the first 2 weeks, followed by 8 to 10 mg/L (days 15–28 after LT), 6 to 8 mg/L (days 29 to 90), and 4 to 6 mg/L (after day 91). If CMV-pp65 antigenemia was noted to be positive, then a dosage of tacrolimus was reduced down to 75% of the regular dosage, and IV GCV (5 mg/kg/dose, every 12 hr) was initiated for the first 2 weeks, followed by a maintenance dose of IV GCV (5 mg/kg/dose, every 24 hr), and the treatment continued until CMV-pp65 antigenemia became negative. If CMV-pp65 antigenemia was indeterminate, immunosuppressive therapy was reduced as far as possible, and CMV-pp65 antigenemia was reevaluated twice a week. We also switched from GCV to valganciclovir (16 mg/kg/dose PO every 12 hr, available from August 2008), which is an oral tablet that was crushed and dissolved in syrup and used as a maintenance therapy when recipients (1) were able to tolerate to oral medication and (2) demonstrated a trend of decrease in CMV-pp65 antigenemia after GCV induction therapy. The dosing of valganciclovir in maintenance was based on the study performed for controlling HCMV disease in infants (*23, 28*). Sodium (100 mg/kg/dose, every 24 hr) was empirically used when CMV-pp65 antigenemia did not improve after decreasing the dose of immunosuppressants and administering a 2- to 3-week course of GCV induction therapy. When sodium was empirically started for possible GCV-resistant CMV, the UL97 genetic sequencing or by an analysis of other known genetic sequences related to resistance was examined (*29*). IV immunoglobulin was used when HCMV disease was not able to be controlled by GCV or sodium.

CMV Serostatus of the Donor and Recipient

The CMV serostatus of donors and recipients was determined by the CMV IgG determined by preoperative enzyme immunoassay. Patients were defined as seropositive if the antibody titer was ≥1:4 and negative if the antibody titer was less than 1:4.

Diagnosis of Acute Rejection and Treatment

Acute rejection was clinically diagnosed on the bases of an increase in liver enzymes (more than three times the upper limit of normal range or an increase of more than 50% over the previous record) with or without histological evidence. Histological diagnosis and grading of acute rejection were performed according to the standardized criteria (*30*). Graft biopsies were considered when other etiologies other than rejection were suspected in clinical course. All the rejection episodes were treated with a corticosteroid bolus injection. Steroid-resistant rejection was treated with additional immunosuppressants, such as mycophenolate mofetil.

Outcome Measures

The primary endpoint of this study was the proportion of recipients with event-free survival 6 months after LT. Events were defined as the occurrence of CMV infection based on the CMV-pp65 antigenemia, active HCMV disease, or death from any cause. HCMV disease was defined when recipients developed the following diseases with positive CMV-pp65 antigenemia; CMV syndrome without any evidence of acute rejection, enterocolitis, pneumonitis, and meningitis.

Statistical Analysis

We used the SPSS 15.0 software package (SPSS, Inc., Chicago, IL) for all analyses. The χ^2 test and Fisher's exact test were used to compare categorical variables between the groups. The Mann-Whitney *U* test and the Kruskal-Wallis test were used to compare continuous variables between two groups and more than three groups, respectively. *P* values were calculated as two trailed and were considered to be significant if *P* less than 0.05.

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Safety and persistence of immunological response 6 months after intramuscular vaccination with an AS03-adjuvanted H1N1 2009 influenza vaccine

An open-label, randomized trial in Japanese children aged 6 months to 17 years

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Key words: adjuvant, H1N1, influenza, japanese children, pandemic

Abbreviations: ATP, according-to-protocol; CBER, center for biologics evaluation & research; CHMP, committee for medicinal products for human use; CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titre; HA, hemagglutinin; HI, hemagglutination inhibition; MAE, medically-attended event; pIMD, potential immune-mediated disease; SAE, serious adverse event; SCR, seroconversion rate; SPR, seroprotection rate; TVC, total vaccinated cohort; VRR, vaccine response rate; WHO, world health organization

This study evaluated the long-term persistence of immune response and safety of two doses of an A/California/7/2009 H1N1 pandemic influenza vaccine adjuvanted with AS03 (an α-tocopherol oil-in-water emulsion-based Adjuvant System) in Japanese children (NCT01001169). Sixty healthy subjects aged 6 mo–17 y were enrolled (1:1) into two study groups to receive 21 d apart, two doses of 1.9 μg haemagglutinin [HA] + $AS03_B$ (5.93 mg α-tocopherol) vaccine (6 mo–9 y) and 3.75 μg HA + $AS03_A$ (11.86 mg α-tocopherol) vaccine (10–17 y), respectively. Immunogenicity data (by haemagglutination inhibition [HI] and microneutralisation assays) to six months after the first vaccine dose are reported here. It was observed that following Dose 2, the HI immune response against the vaccine homologous strain induced by the two different dosages of the AS03-adjuvanted vaccine met and exceeded the US and European regulatory guidance criteria for pandemic influenza vaccines (seroprotection rate [SPR]/seroconversion rate [SCR]: 100%/100%; geometric mean fold rise GMFR: 146.8/57.1). Further, the immune response persisted for at least six months after the first vaccine dose wherein these regulatory criteria were still met (SPR: 100%/100%; SCR: 96.4%/89.7%; GMFR: 25.3/23.5). The neutralising antibody response was comparable to the HI immune response at Day 42 (vaccine response rate [VRR]: 100%/100%) and at Day 182 (VRR: 96.4%/82.8%). Overall, both vaccine dosages had a clinically acceptable safety profile. Thus, two doses of a 1.9 μg or 3.75 μg HA AS03-adjuvanted H1N1 2009 pandemic influenza vaccine in children aged 6 mo–17 y induced strong immune responses against the vaccine homologous strain that persisted for at least six months after the first vaccine dose.

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