Immunoglobulin prophylaxis prevents hospital admissions for fever in pediatric acute lymphoblastic leukemia: results of a multicenter randomized trial

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Supplementary data

Study centers

Vrije Universiteit University Medical Center, Amsterdam

Amsterdam University Medical Center, Emma Children's hospital, Amsterdam

University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht

University Medical Center Groningen, Beatrix Children's Hospital, Groningen

Erasmus Medical Center, Sophia Children's Hospital, Rotterdam

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Definition of MR group, in- and exclusion criteria

MR was defined as patients with newly diagnosed ALL with minimal residual disease (MRD) positivity based on molecular assays, at day 33 and/or day 79 of treatment, but MRD at day 79 of treatment $<10^{-3}$, or in case of either inconclusive/missing MRD results, and absence of high risk criteria.[3] Exclusion criteria were: underlying immune deficiency present before diagnosis of ALL, history of anaphylactic reactions to plasma products, IgA deficiency, history of thrombo-embolism, trisomy 21, fungal infections diagnosed before start of treatment with IVIG, history of renal insufficiency, patients with parents who are not able to understand or answer the questionnaires, pregnancy or unwillingness to use adequate contraceptive measures in females with child bearing potential.

Starting criteria for IVIG infusion

Clinical criteria that had to be met before every IVIG infusion, were: absence of clinical signs of renal failure, absence of diabetic ketoacidosis, absence of acute thrombo-embolic problems, no post-surgery immobilization, absence of clinical signs

of respiratory or circulatory insufficiency, no use of loop diuretics. In case of fever (defined as temperature ≥38.5^{o}C), IVIG infusion was postponed on the first day of fever. In case that IVIG infusion had to be postponed for clinical reasons, IVIG infusion was postponed until the clinical condition of the patient had recovered at the judgement of the treating physician. In case of repeatedly high serum IgG levels (>16 g/L), IVIG dose was decreased with 50% until levels <10 g/L were reached, then the starting dose of 0.7 g/kg was reintroduced.

Criteria for IVIG in control group

When there was an IgG level ≤6 g/L in the first 19 weeks of ALL MR therapy, or ≤4 g/L thereafter, in combination with either one of the following: history of ≥4 admissions for infection; or 1 central nervous system infection; or 1 infection requiring ICU admission, patients in the control group were allowed to receive IVIG. After receiving IVIG once, a new indication occurred when there was an IgG level ≤6 g/L (or ≤4 g/L after 19 weeks of MR therapy) in combination with a history of ≥2 admissions for infection; or 1 central nervous system infection; or 1 infection requiring ICU admission.

Data collection

Hospital records were checked against a parental study diary registering fever episodes in order not to miss any admissions for fever. Subsequently, detailed information of the admissions for fever was recorded in case report forms (CRFs): blood culture results, suspected cause of fever, start of empirical antibiotic therapy, chemotherapy adaptation in relation to the admission for fever, and ICU admission. Chemotherapy adaptation was defined as chemotherapy disrupted or dosage decreased because of this admission for fever. IgG levels were measured before start of the trial and at regular intervals thereafter.

Sample size calculation

A negative binomial distribution was used to compute the number of patients needed to detect a reduction of 50% admissions for fever, since the distribution for admissions for fever shows overdispersion (known from DCOG ALL-10 study[2]). Monte Carlo simulations with 10000 replications yielded 70 patients per arm with power equal to 80% and one-sided test with alpha 5%. Details about the power analysis are reported in the protocol (trial registration number: EudraCT 2012-000067-25, NL3227 (clinicaltrialregister.nl)).

Supplementary table S1: Reported adverse events for the IVIG prophylaxis and control group.

(S)AE	IVIG	CTCAE grade	Control	CTCAE grade
Allergic reaction/Anaphylaxis	2	III-IV	1	IV
Gastro-intestinal toxicity	17	III-IV	13	I-IV
Gastrointestinal bleeding	1		0	
Gastrointestinal colitis	0		1	
Gastrointestinal constipation	1		1	
Gastrointestinal diabetes	1		3	
Gastrointestinal other	1		1	
Gastrointestinal pancreatitis	10		3	
Gastrointestinal perforation	1		0	
Liver failure	1		2	
Veno-occlusive disease	1		2	
Infections	17	III-IV	14	III-V
Infection bacterial	5		5	
Infection fungal	7		7	
Infection pneumocystis jerovecii (carini)	3		1	
Infection unknown origin	2		0	
Infection viral	0		1	
Neurotoxicity	14	II-IV	8	II-IV
Central neurotoxicity convulsion	5		3	
Central neurotoxicity encephalopathy	4		3	
Central neurotoxicity other	3		2	

Peripheral neurotoxicity	2		0	
Thrombosis	14	II-IV	2	III-IV
Thrombosis cerebral	7		2	
Thrombosis peripheral	7		0	
Other	12	II-IV	8	II-IV
Bleeding	1		0	
Electrolyte disorder	2		0	
Fracture	0		1	
Hypertension	0		2	
Hypoglycemia	4		1	
Kidney failure	1		0	
Other	4		3	
Pneumothorax	0		1	
Total	76		46	

Supplementary Table S2

Estimates regression coefficient, adjusted for age, of effect of IVIG on outcomes, obtained with a negative binomial model.

	Overall			**Maintenance phase**		
Outcome	**Coefficient**	**Standard Error**	**p-value**	**Coefficient**	**Standard Error**	**p-value**
Intention-to-treat analyses						

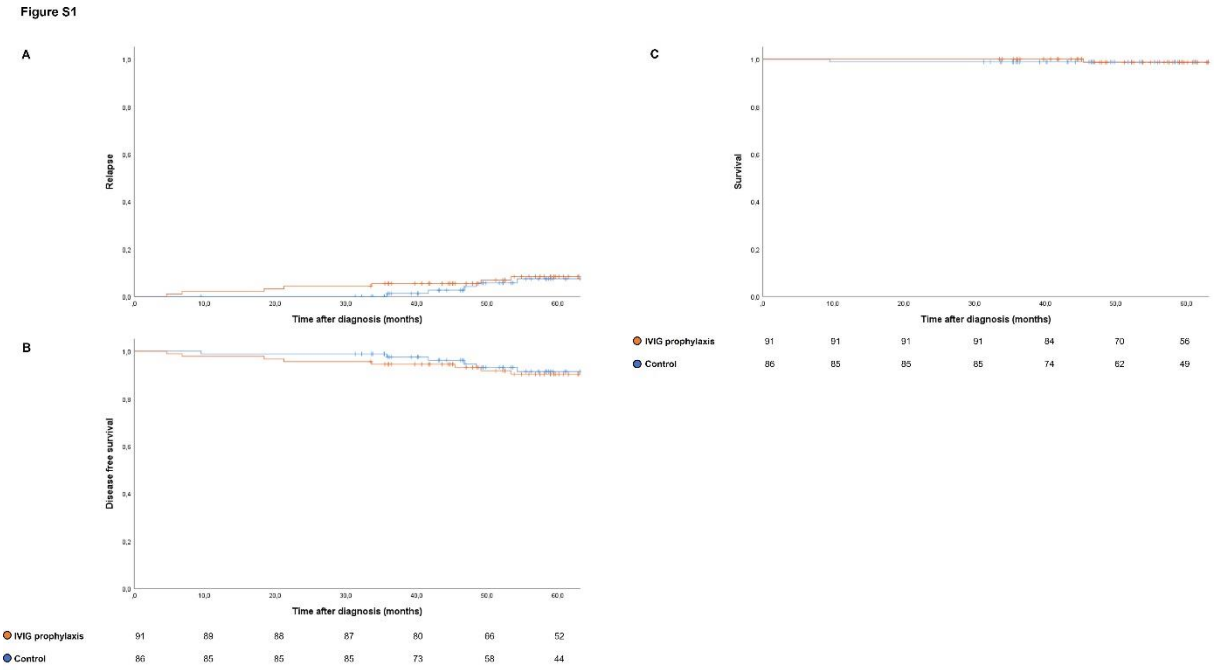
Admissions for fever	-0.321	0.126	0.011	-0.566	0.168	<0.001
Fever in neutropenia	-0.359	0.149	0.016	-0.814	0.207	<0.001
Negative blood cultures	-0.624	0.152	<0.001	-0.951	0.209	<0.001
Empirical antibiotic therapy	-0.298	0.134	0.030	-0.626	0.188	<0.001
Adaptation in chemotherapy	-0.456	0.154	0.003	-0.675	0.197	<0.001
Per-protocol analyses						
Admissions for fever	-0.299	0.132	0.024	-0.541	0.172	0.002
Fever in neutropenia	-0.312	0.155	0.040	-0.800	0.212	<0.001
Negative blood cultures	-0.618	0.159	<0.001	-0.884	0.215	<0.001
Empirical antibiotic therapy	-0.313	0.144	0.029	-0.638	0.192	<0.001
Adaptation in chemotherapy	-0.447	0.159	0.005	-0.669	0.200	<0.001

Supplementary Table S3

Estimates regression coefficient, for different age groups on admissions for fever, obtained with a negative binomial model.

Outcome	Overall			Maintenance phase		
	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value
Intention-to-treat analyses						
Age 1-4 years	reference					
Age 5-9 years	-0.615	0.145	<0.001	-0.760	0.193	<0.001
Age 10-14 years	-1.150	0.214	<0.001	-1.473	0.308	<0.001
Age 15-18 years	-1.188	0.265	<0.001	-1.527	0.386	<0.001
Per-protocol analyses						
Age 1-4 years	reference					
Age 5-9 years	-0.608	0.149	<0.001	-0.759	0.192	<0.001
Age 10-14 years	-1.273	0.234	<0.001	-1.603	0.332	<0.001
Age 15-18 years	-1.271	0.299	<0.001	-1.456	0.405	<0.001

Supplementary Figure S1



Relapse (A), Disease free survival (B), and Overall survival (C) curves for IVIG prophylaxis in orange and control group in blue. Relapse was not corrected for competing events, as there was only one death without relapse.