Advanced therapy: The future of BMT in Asia

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19-20 NOVEMBER 2022
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HCT for non-malignant disorders increased

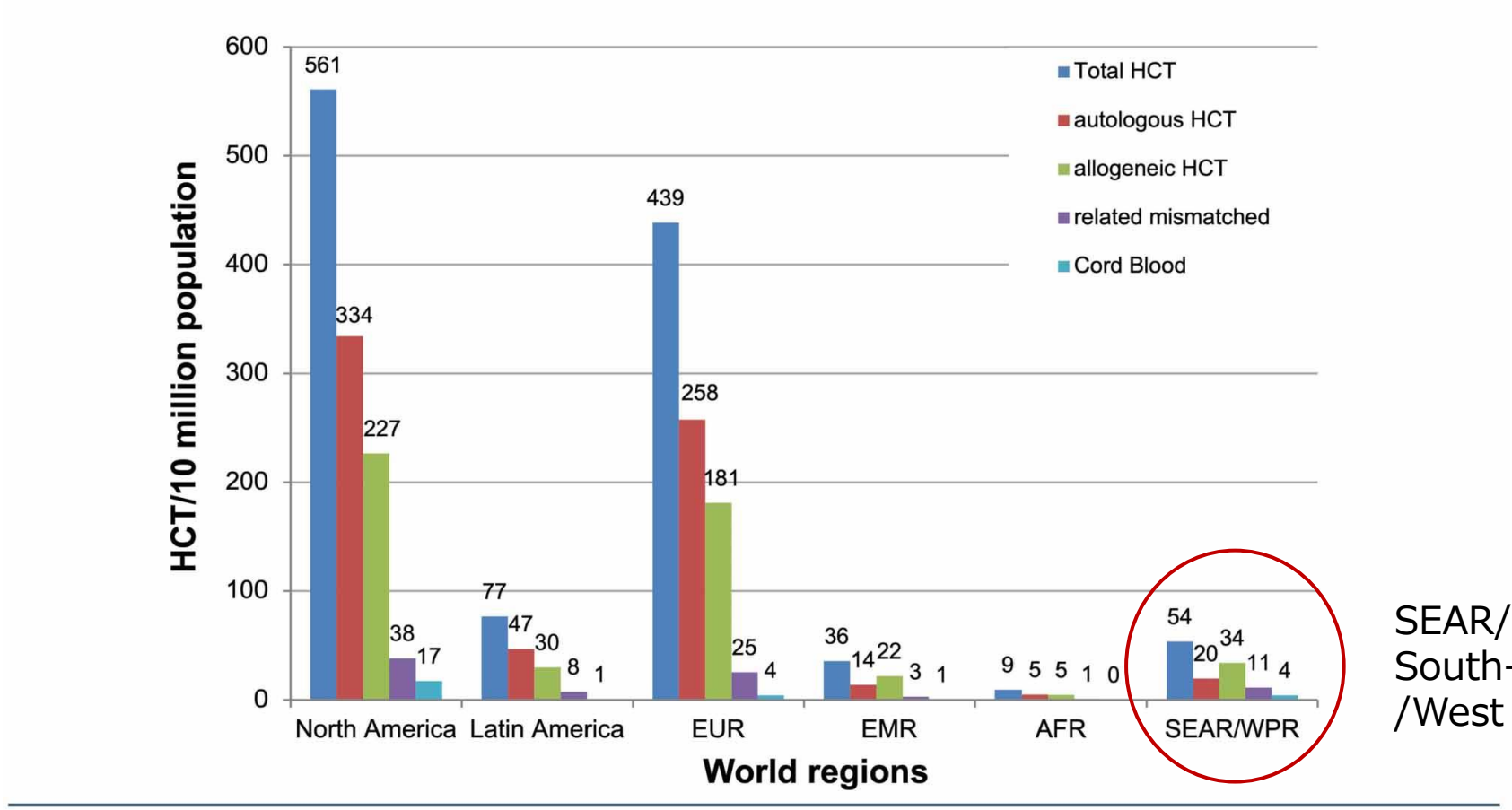
Table 1. Global hematopoietic cell transplantation (HCT) activity in 2006, 2016 and changes according to disease indication, donor type and world region.

	Family			Unrelated			Allogeneic			Autologous			Total			
	2006	2016	Δ % (06-16)	2006	2016	Δ % (06-16)	2006	2016	Δ % (06-16)	2006	2016	Δ % (06-16)	2006	2016	Δ % (06-16)	2016 %
Leukemias	7,491	14,992	100	6,901	13,727	99	14,392	28,719	99.5	1,726	844	-51.1	16,118	29,563	83.4	35.7
AML	3,587	7,531	110	3,024	6,803	125	6,611	14,334	116.8	1,269	631	-50.3	7,880	14,965	89.9	18.1
ALL	1,679	3,965	136	1,809	2,930	62	3,488	6,895	97.7	209	155	-25.8	3,697	7,050	90.7	8.5
CML	826	624	-24	508	484	-5	1,334	1,108	-16.9	14	1	-92.9	1,348	1,109	-17.7	1.3
MDS/MPS	1,052	2,472	135	1,216	3,144	159	2,268	5,616	147.6	59	10	-83.1	2,327	5,626	141.8	6.8
CLL	295	220	-25	261	240	-8	556	460	-17.3	173	22	-87.3	729	482	-33.9	0.6
Other leukemias	52	180	246	83	126	52	135	306	126.7	2	25	1,150.0	137	331	141.6	0.4
LPD	1,863	2,023	9	1,356	1,949	44	3,219	3,972	23.4	21,655	39,878	84.2	24,874	43,850	76.3	53.0
Plasma cell disorders	490	312	-36	283	348	23	773	660	-14.6	10,675	23,701	122.0	11,448	24,361	112.8	29.5
HD/NHL	1,373	1,673	21	1,073	1,573	47	2,446	3,246	32.7	10,980	16,103	46.7	13,426	19,349	44.1	23.4
Lymphoma other/unknown	0	38		0	28		0	66		0	74		0	140		0.2
Solid tumors	110	47	-57	40	37	-7	150	84	-44,0	2,560	2,853	11.4	2,710	2,937	8.4	3.6
Non-malignant disorders	1,458	3,423	134	902	2,004	122	2,360	5,427	139.4	193	691	258.0	2,553	6,118	139.6	7.3
Bone marrow failures	840	1,775	111	452	909	101	1,292	2,684	107.7	0	6		1,292	2,690	108.2	3.3
Hemoglobinopathies	338	962	185	54	301	457	392	1,263	222.2	3	10	233.3	395	1,273	222.3	1.5
Immune deficiencies	206	472	129	239	500	109	445	972	118.4	3	15	400.0	448	987	120.3	1.2
Inherited diseases of metabolism	59	111	88	118	182	54	177	293	65.5	2	4	100.0	179	297	65.9	0.4
Autoimmune disorders	6	19	217	10	22	120	16	41	156.3	184	637	246.2	200	678	239.0	0.8
Other non-malignant disorders	9	84	833	29	90	210	38	174	357.9	1	19	1,800.0	39	193	394.9	0.2
Others	80	109	36	132	114	-14	212	223	5.2	96	27	-71.9	308	250	-18.8	0.3
EUR	4,906	7,074	44	4,222	8,348	98	9,128	15,422	69.0	15,088	21,946	45.5	24,216	37,368	54.3	45.2
North America	2,580	3,680	42.6	2,878	4,458	54.9	5,458	8,138	49.1	6,730	12,006	78.4	12,188	20,144	65.3	24.4
SEAR/WPR	1,948	7,392	279	2,110	4,513	114	4,058	11,905	193.4	3,038	6,884	126.6	7,096	18,789	164.8	22.7
Latin America	771	1,197	55.3	115	438	280.9	886	1,635	84.5	947	2,561	170.4	1,833	4,196	128.9	5.1
EMR/AFR	797	1,251	57	6	74	1,133	803	1,325	65.0	427	896	109.8	1,230	2,221	80.6	2.7
TOTAL	11,002	20,594	87.0	9,331	17,831	91.0	20,333	38,425	89.0	26,230	44,293	68.9	46,563	82,718	77.6	100

Δ (06/16) Difference from 2006 to 2016 in %; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MDS/MPS: myelodysplastic syndrome/myeloproliferative syndrome; CLL: chronic lymphocytic leukemia; LPD: lymphoproliferative disorders; EUR: Europe; SEAR/WPR: South East Asia Pacific Region/West Pacific Region; EMR/AFR: East Mediterranean Region/African Region.

Niederwiser D. Haematologica 2022.

HCT rates are low in Asia



SEAR/WPR
South-East Asia Pacific Region /West Pacific Region.

Figure 1. Transplant rates. Hematopoietic cell transplantation (HCT)/10 million population according to transplant type (autologous, allogeneic, related mismatched and cord blood) and world regions in 2016. EUR: Europe, EMR: East Mediterranean Region; AFR: Africa; SEAR/WPR: South East Asia Pacific Region/West Pacific Region.

Niederwiser D. Haematologica 2022.

Advances in HCT in the Asia-Pacific region

Table 2 Number of HSCTs performed according to stem cell source in 2015

	Related				Unrelated						
	BM	PB	CB	Multiple	BM	PB	CB	Multiple	Related/Unrelated	BM Bank	CB Bank
Australia	40	181	1	0	57	255	41	0	0.6	+	+
Bangladesh	0	0	0	0	0	0	0	0	NA	–	–
China	26	1082	34	1369	1	439	125	7	4.4	+	+
Hong Kong	25	36	0	1	24	27	6	0	1.1	+	+
India	144	775	1	15	3	64	10	0	12.1	+	+
Iran	16	263	2	0	4	16	0	0	14.1	+	+
Japan	301	932	0	10	1175	55	1251	0	0.5	+	+
Korea	63	689	0	3	8	475	53	0	1.4	+	+
Malaysia	28	124	0	2	9	14	1	0	6.4	+	+
Myanmar	0	0	0	0	0	0	0	0	NA	–	–
New Zealand	4	35	0	0	5	33	8	0	0.8	+	+
Pakistan	72	37	0	15	0	0	0	0	NA	–	–
The Philippines	0	15	0	0	0	0	0	0	NA	–	–
Singapore	5	58	0	0	2	26	10	0	1.7	+	+
Sri Lanka	6	0	0	0	0	0	0	0	NA	–	–
Taiwan	5	142	0	23	3	130	3	0	1.3	+	+
Thailand	1	18	0	3	0	3	0	0	7.3	–	+
Vietnam	0	38	1	0	0	0	6	0	6.5	+	+
Total	736	4425	39	1441	1291	1537	1514	7	1.5		

BM bone marrow, *PB* peripheral blood, *CB* cord blood, *HSCT* hematopoietic stem cell transplantation

Ida M. BMT 2019.

- ✓ More unrelated donors in Australia, Japan and NZ
- ✓ PBSCT > BMT
- ✓ Multiple stem cell sources in China
- ✓ 83% of CBT in Japan
- ✓ BM and CB banks are in limited countries

Correlation between HCT and GDP

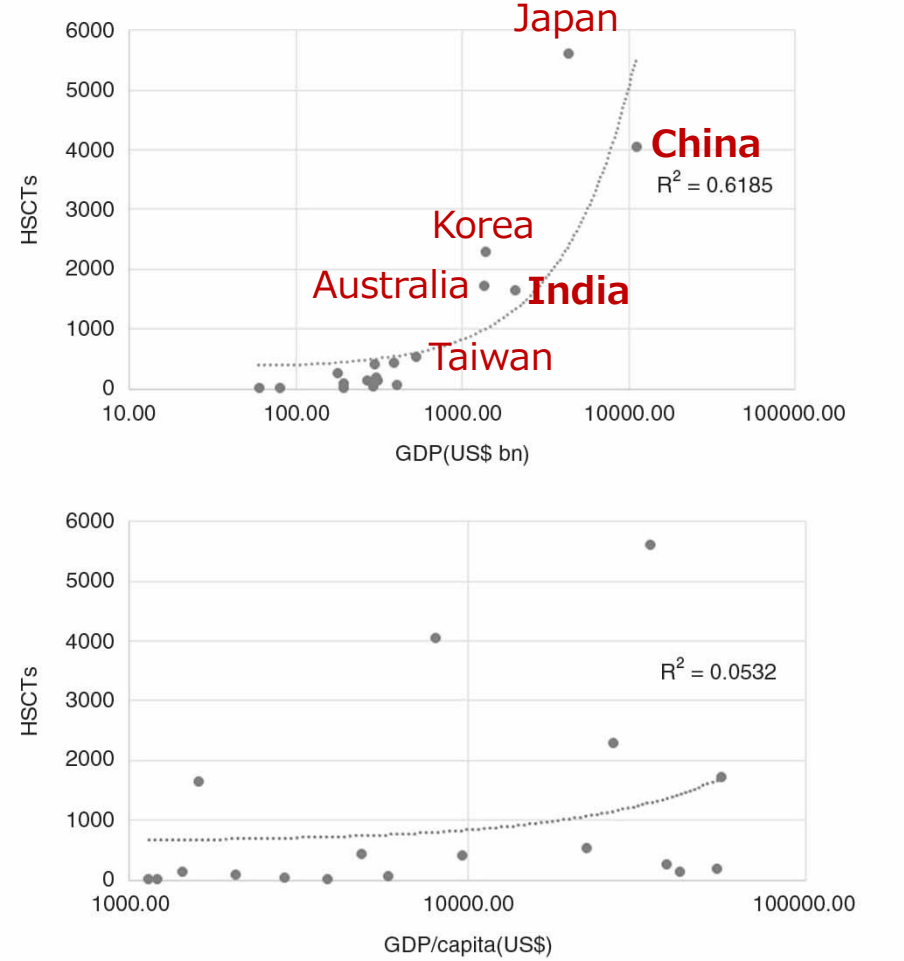
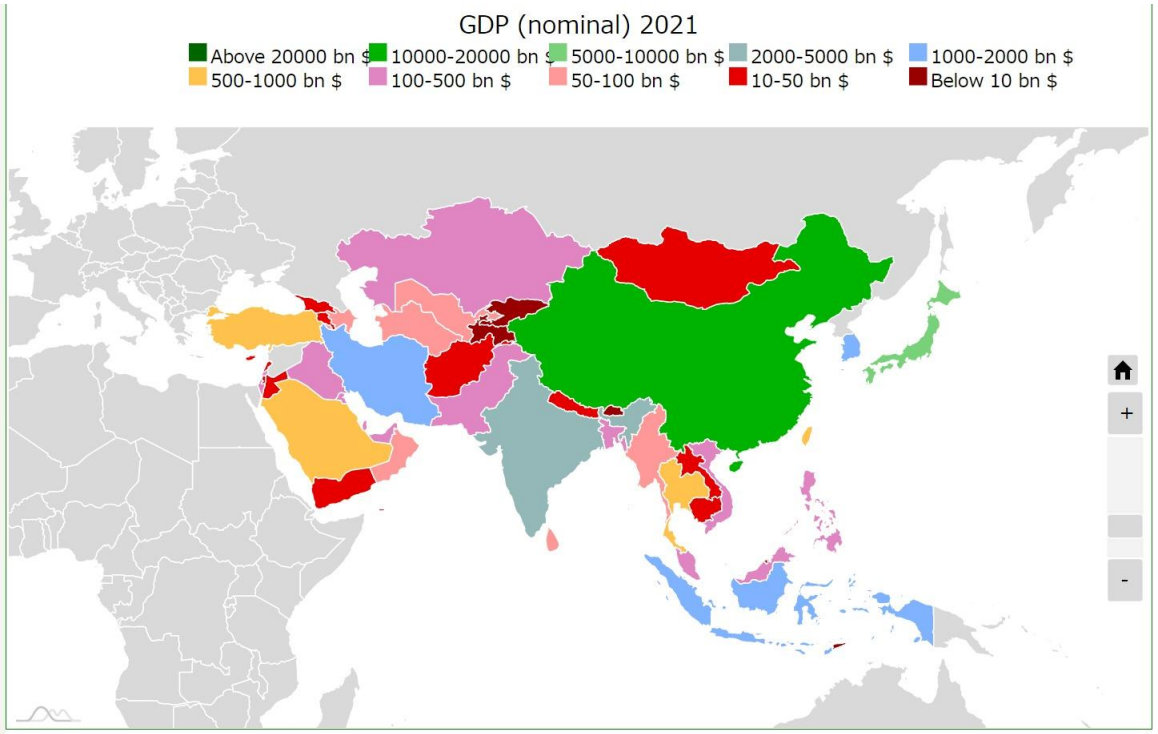


Fig. 4 Correlation between absolute numbers of transplants and the gross domestic product (GDP, top) and (bottom)

Recent remarkable economic growth and advances in medical services in **China** and **India**



GDP of Asian countries 2021 - StatisticsTimes.com

Ida M. BMT 2019.

Which diseases?

Hematopoietic Stem Cell Transplantation in Primary Immunodeficiency Diseases: Current Status and Future Perspectives

*Riccardo Castagnoli[1,2], Ottavia Maria Delmonte[1], Enrica Calzoni[1,3] and Luigi Daniele Notarangelo[1]**

TABLE 2 | Indications for HSCT in PID.

HSCT curative	HSCT partially curative	HSCT controversial
SCID	Cartilage Hair Hypoplasia	CVID
CID^	PGM3 deficiency	Agammaglobulinemia
CGD	STAT1-GOF	Complement deficiencies (other than C1q deficiency)
DOCK8 deficiency	STAT3- GOF	DGS
DOCK2 deficiency	Severe congenital neutropenia	IKBA deficiency
IPEX	ADA2 deficiency	NEMO deficiency
WAS	CIQ deficiency	
WIP deficiency	CD25 deficiency	
ARPC1B deficiency	IL-10 deficiency	
CD40 ligand deficiency	IL-10 Receptor deficiency	
CD40 deficiency	DNA double-strand break repair disorders	
XLP1, XLP2		
APDS		
MHC Class II deficiency		
AD Hyper IgE syndrome		
CTLA4 haploinsufficiency		
LRBA deficiency		
Familial HLH types 1–5		
GATA2 deficiency		
RAB27A deficiency		
LAD I		
Reticular Dysgenesis		

Front Pediatr 2019.

Disease/Patient Consideration

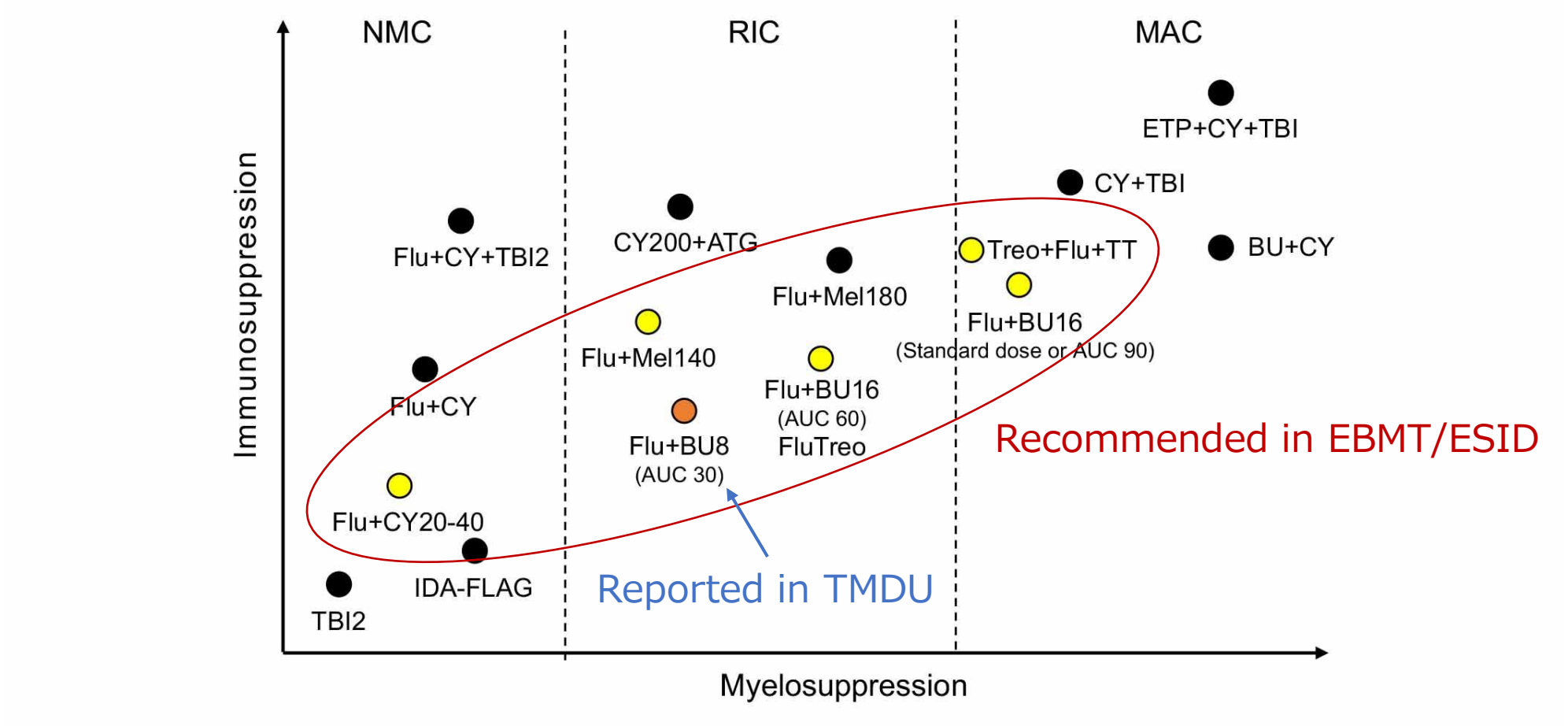
- Unknown/Unclear natural history
- Lack of long-term follow-up studies
- Changing **therapeutic landscape**
- Incomplete penetrance/phenotypic heterogeneity
- Symptomatic patients with VUS on genetic sequencing

When is it OK to wait for HCT?

HSCT consideration

- Unknown/unclear outcome following HSCT
- Changing **therapeutic landscape**
  - availability of alternative therapies and/or bridging therapies
- Co-morbidities
- Fertility
- Impact on life of HSCT process

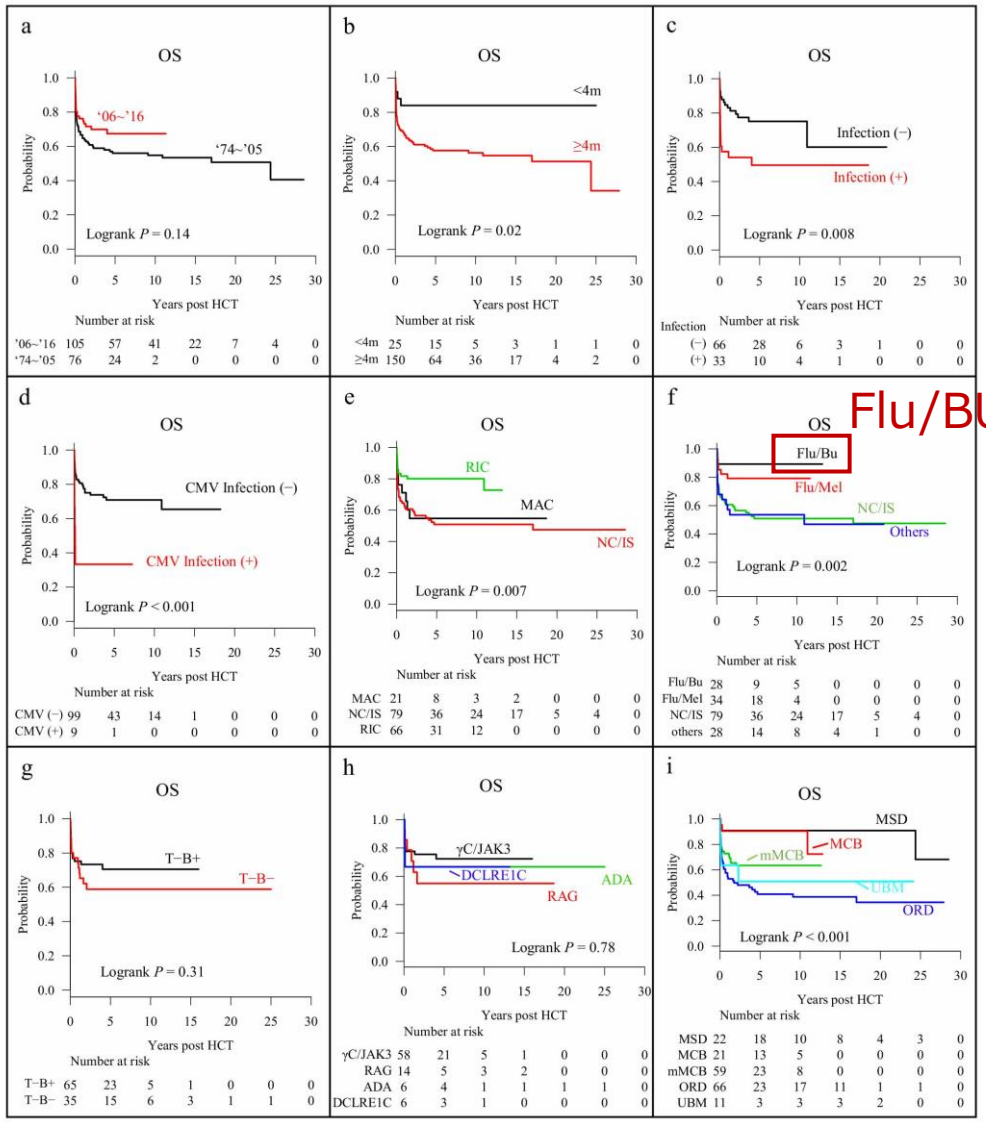
Intensity of conditioning regimen for HCT



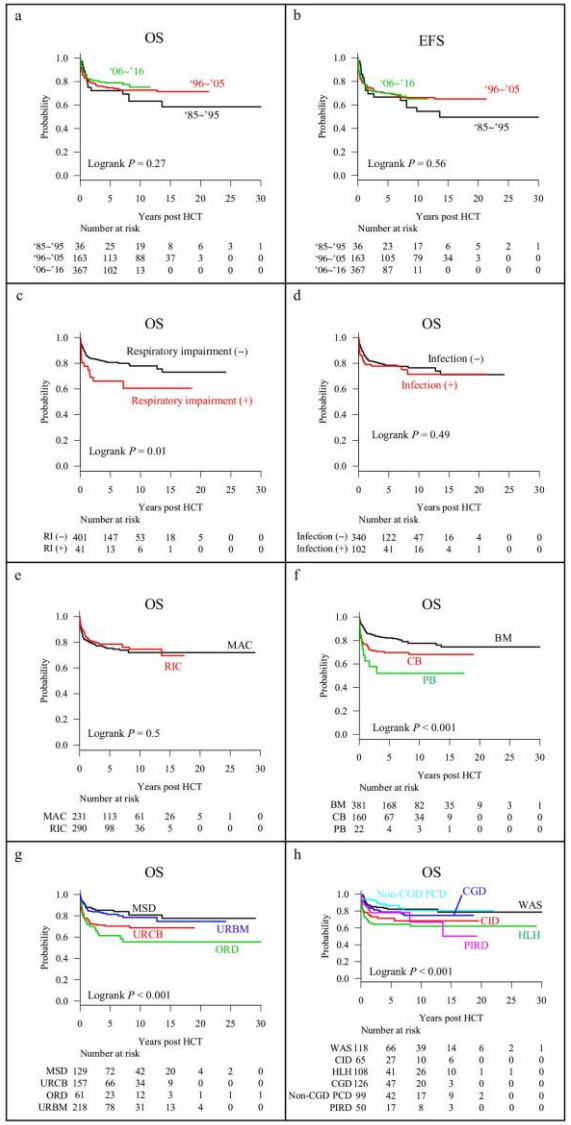
Nishimura A. Int J Hematol 2022.

Japanese retrospective study of HCT for PID

SCID



Other than SCID



Flu/BU is better outcome

Miyamoto S. J Clin Immunol 2021.

Miyamoto S. J Clin Immunol 2022.

Journal of Clinical Immunology (2021) 41:89–98
https://doi.org/10.1007/s10875-020-00888-2

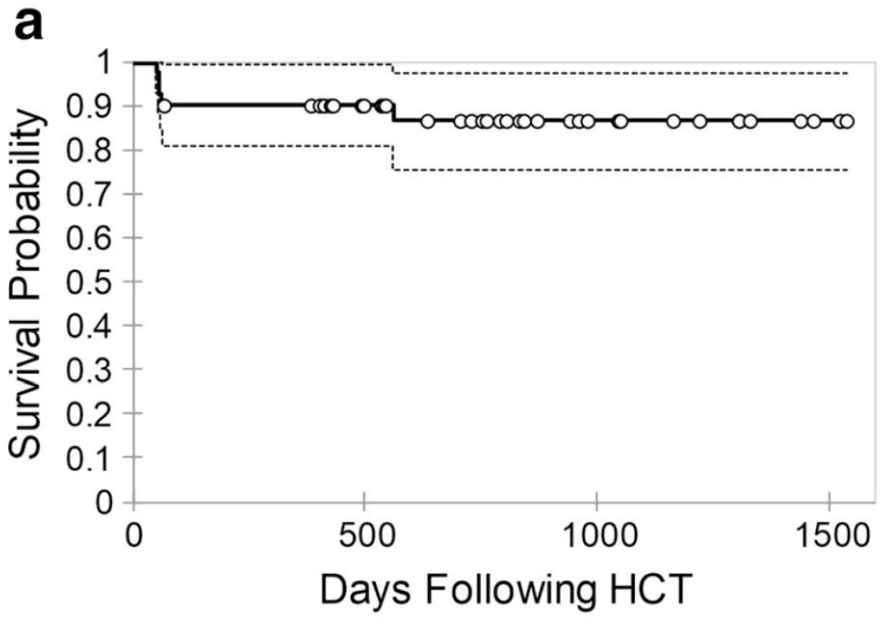
ORIGINAL ARTICLE

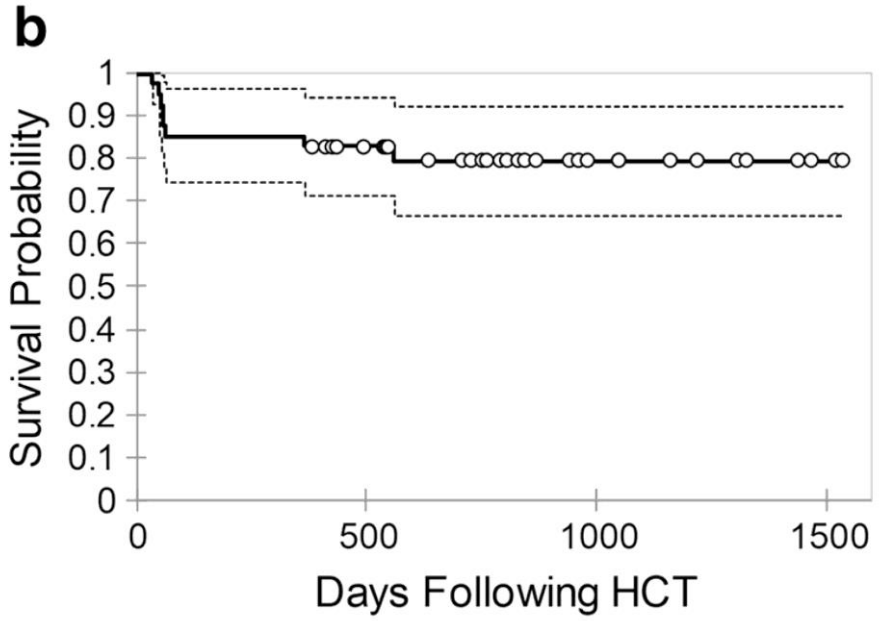
Experience with a Reduced Toxicity Allogeneic Transplant Regimen for Non-CGD Primary Immune Deficiencies Requiring Myeloablation

Sharat Chandra[1,2] · Shanmuganathan Chandrakasan[3] · Blachy J. Dávila Saldaña[4] · Jack J. Bleesing[1,2] · Michael B. Jordan[1,2] · Ashish R. Kumar[1,2] · Michael S. Grimley[1,2] · Christa Krupski[1,2] · Stella M. Davies[1,2] · Pooja Khandelwal[1,2] · Rebecca A. Marsh[1,2]

Alemtuzumab
Fludarabine
Target BU (AUC 60-65 mg/L x h)

Non-TBI
Reduce post HSCT-HLH
but
Slow T-cell reconstitution
High risk for viral infection

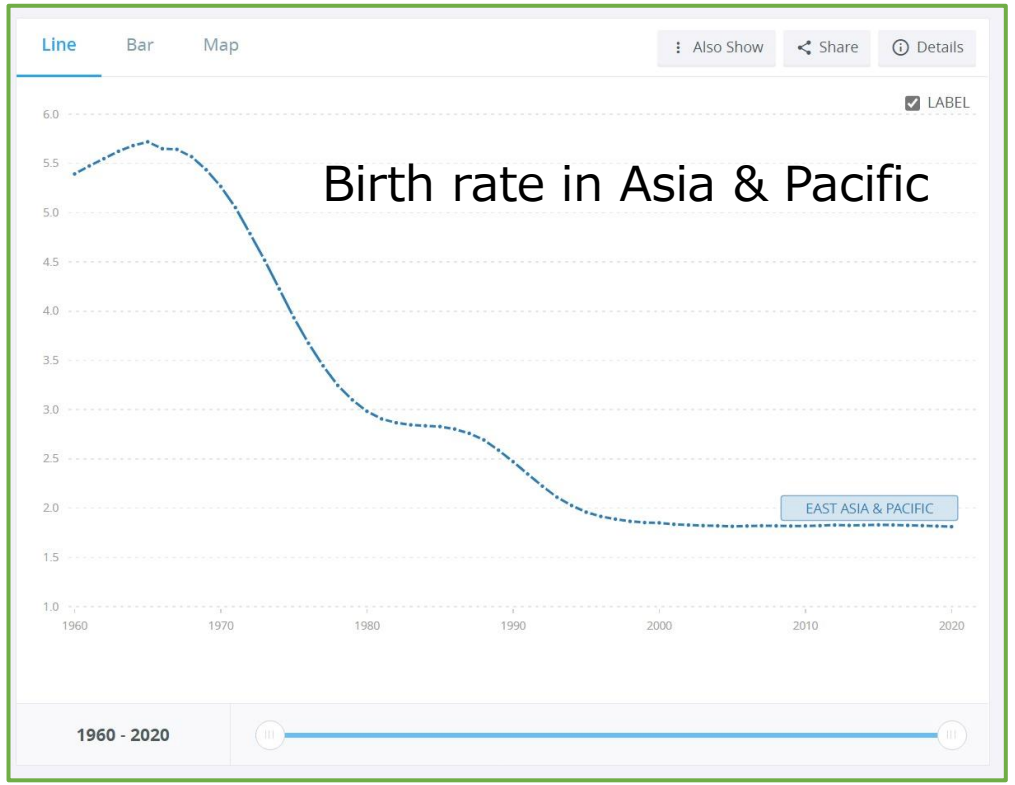




Birth rate↓ → Siblings↓
International marriage↑

HLA-matched donors in BM and CB banks

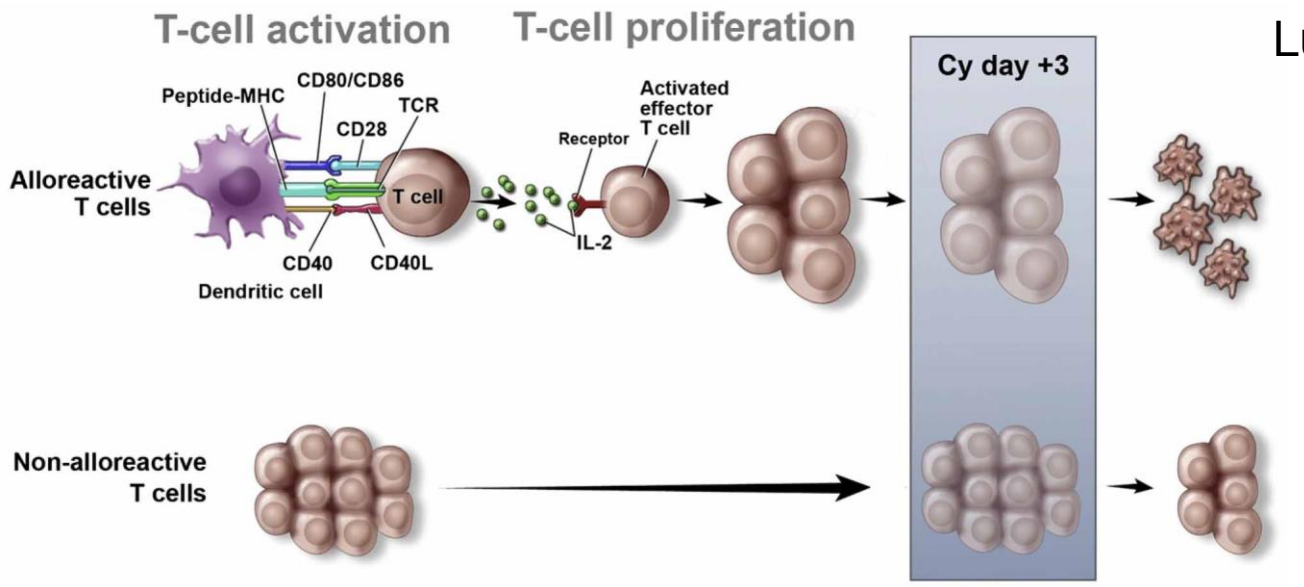
Haploidentical HSCT
Acute/chronic GVHD↑→ADL/QOL↓
RRT↑→OS↓



https://data.worldbank.org/indicator/SP.DYN.TFRT.IN?locations=Z4

- Post-transplant cyclophosphamide (PT-Cy) haploidentical HCT
- TCRαβ/CD19-depleted HCT

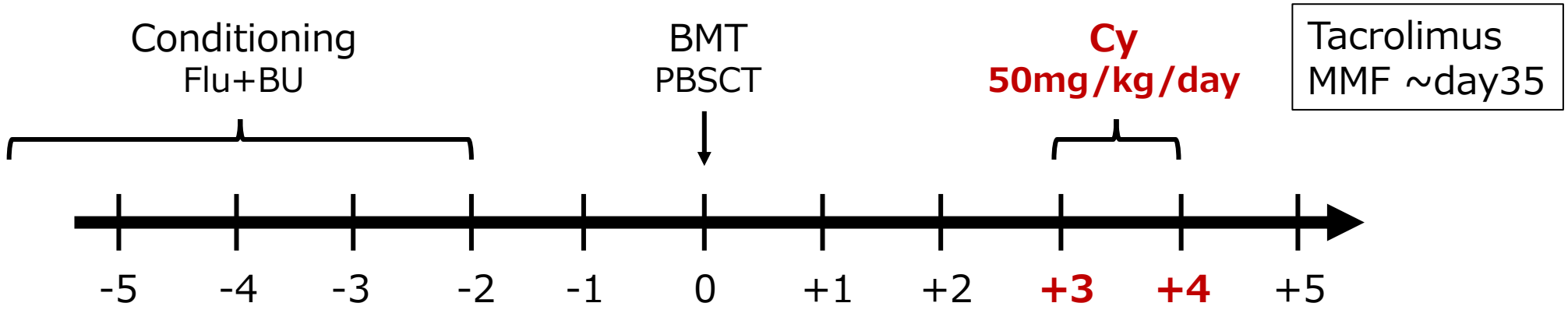
PT-Cy haploidentical HCT



Luznik L, Fuchs EJ. Immunol Res 2010.

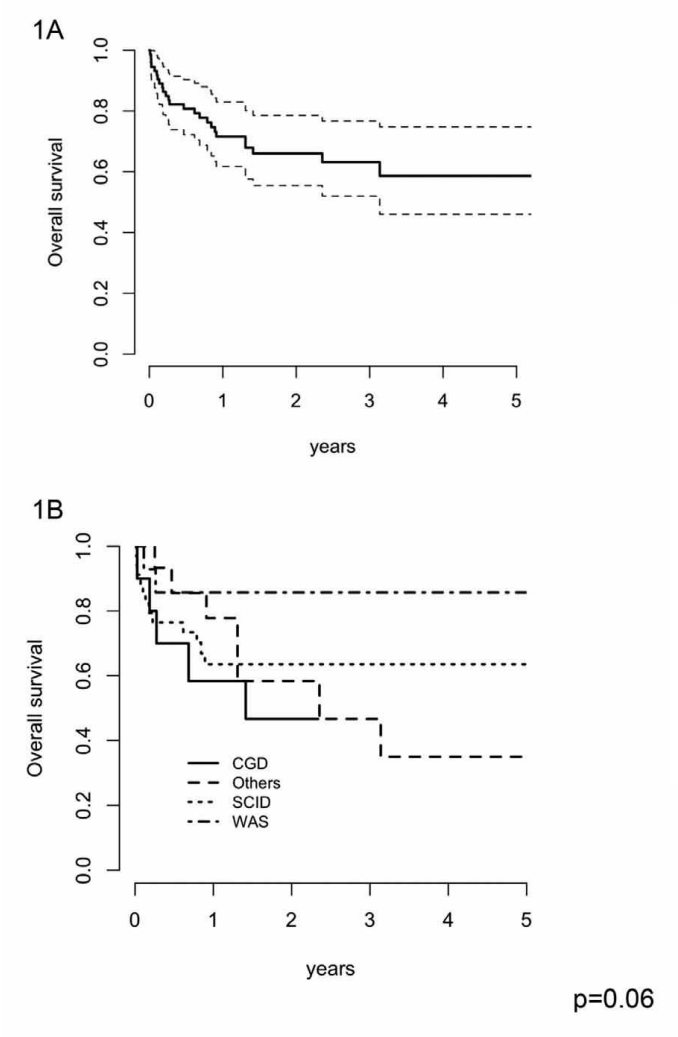
GVHD↓

Enriched HPC



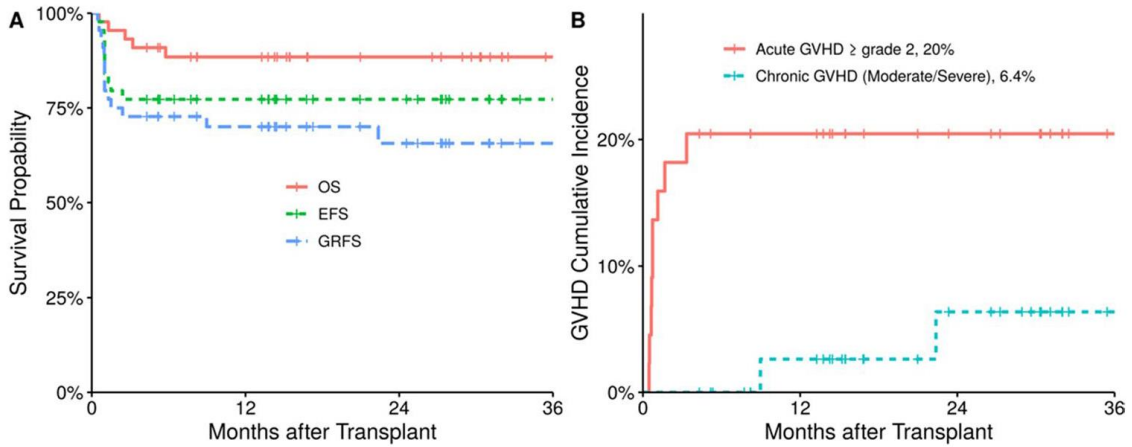
PT-Cy Haplo HCT for patients with PID

Brazil



Fernandes JF. BBMT 2020.

Jordan



Hashem H. J Clin Immunol .

Patients' characteristics

Character		n
Disease (n=14)		
	X-linked lymphoproliferative disease type2 (XIAP def.)	5
	X-linked lymphoproliferative disease type1 (SAP def.)	2
	Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID, NEMO def)	2
	Activated phosphoinositide 3-kinase delta syndrome type1 (APDS1)	1
	Activated phosphoinositide 3-kinase delta syndrome type2 (APDS2)	1
	Familial hemophagocytic lymphohistiocytosis type3 (FHL3)	1
	Leukocyte adhesion deficiency type1 (LAD-I)	1
	Wiskott–Aldrich syndrome	1
Age at HCT	median (range)	7 y (4m~15y)
Observation period	median (range)	298 days (158–503 days)
Active infection at HCT		
	Yes	7 (CMV 4, bacterial infection w/ unknown focus 2, pneumonia 1, NTM/HBV 1)
	No	7
Non-infection Complication at HCT		
	None	6
	Inflammatory bowel disease	3 (XIAP def.)
	Hemophagocytic lymphohistiocytosis (HLH)/ HLH-like symptoms	3 (XIAP, SAP, FHL3)
	Granulomatous and lymphocytic interstitial lung disease	1 (XIAP)
	Rejection after 1st HCT	1 (EDA-ID)
Performance status		
	0-1	11
	2-4	3

Donor, GVHD Prophylaxis, and Conditioning

Character		n
Donor ; GVHD prophylaxis		
	Parent (haplo); Tac+**PT-CY**+MMF	8
	Parent (haplo); Tac+sMTX+PT-CY (2nd HCT after rejection)	1
	MSD ; CSA+sMTX	2
	URBM (8/8 matched); Tac+sMTX	3
Conditioning		
	Flu 180+BU (AUC [hr*mg/L] median, range)	12 (**65**, 58.3–65.6)
	Flu 120 (2nd HCT after rejection)	1
	Flu 180+TT 8+Mel 140	1
Alemtuzumab dose		
	0.16mg/kg×5 days (total **0.8** mg/kg)	12
	4 days (total 0.496 mg/kg)	1
	0.16mg/kg×3days (total 0.48 mg/kg)	1
Steroid prophylaxis for CRS		
	mPSL	13
	mPSL+HDC	1

days	-14	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1
Alem		○	○	○	○	○								
Flu						△	△	△	△	(△	△)			
Bu										■	■	■	■	

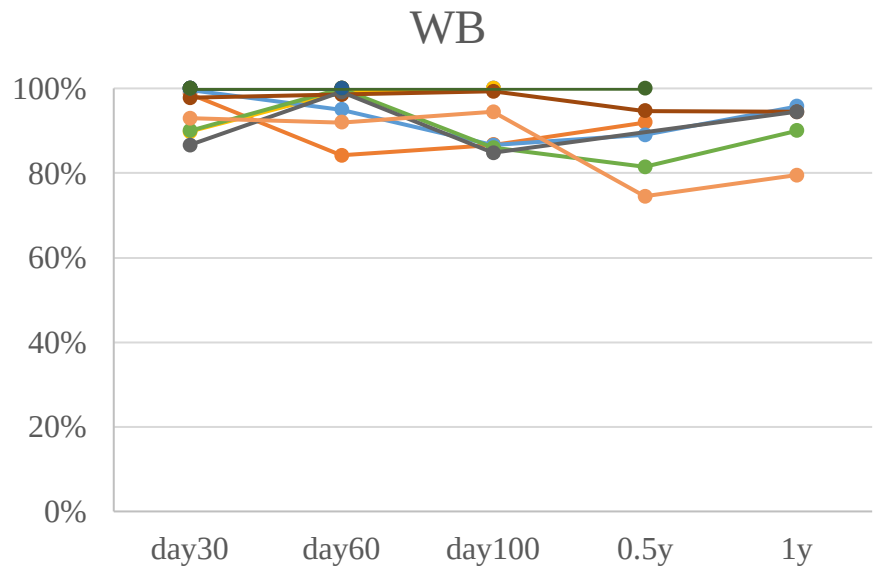
Major Outcomes

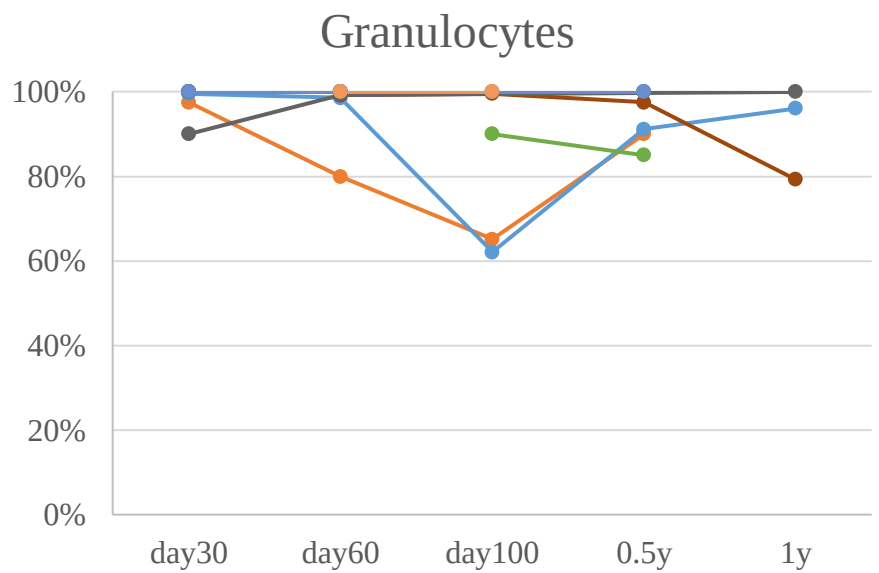
Outcomes		
Survival (follow-up; median, range)		
	Yes	**14** (298 days, 158–503 days)
Neutrophil Engraftment		
	Yes, median days (range)	14, 19.5 days (12–47)
Platelet Engraftment (>20,000/μL)		
	Yes, median days (range)	14, 28 days (16–71)
Secondary graft failure (n=14)		
		None
Acute GVHD		
	No	8
	Yes	**6**
	grade 1	4 (skin I×3、skin Ⅱ×1)
	grade 2	2 (skin III/gut I×1, skin II/gut I×1)
Chronic GVHD		
	No	12
	Yes, limited	**2**

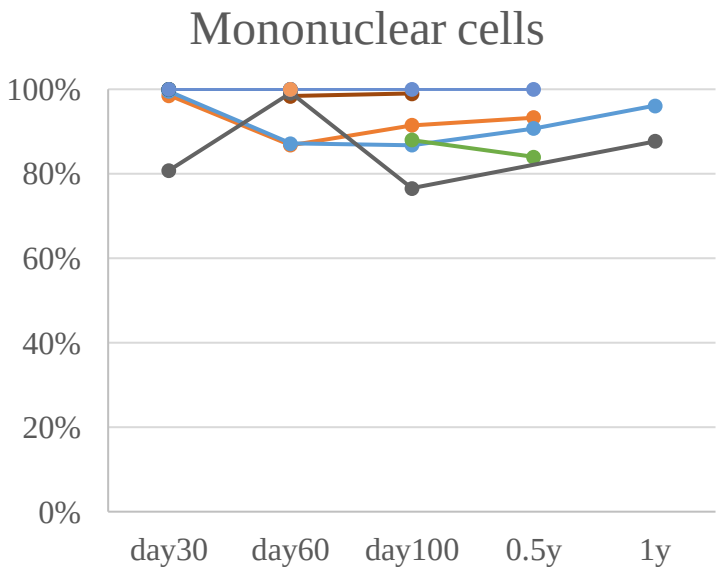
All the patient survived
No grade III-IV aGVHD or extensive cGVHD

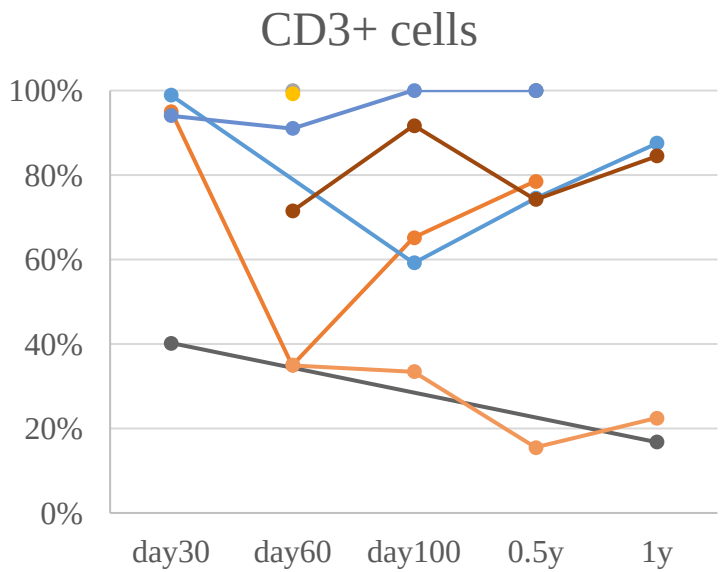
T-cell reconstitution is poor

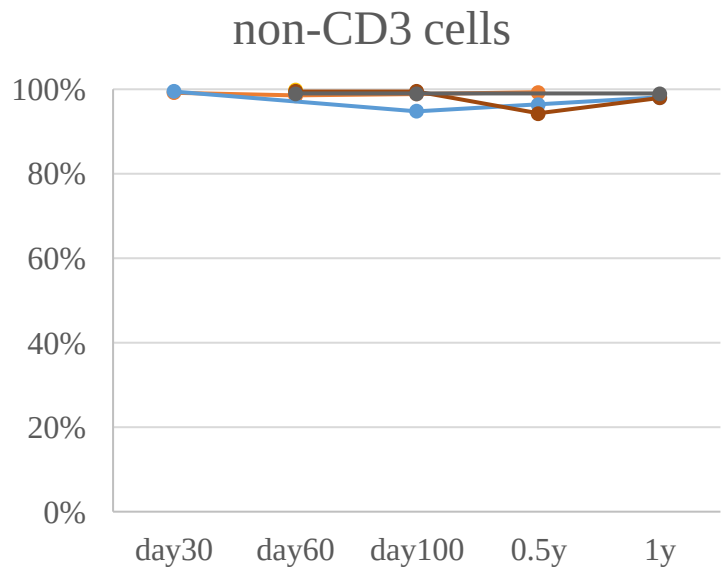
Donor chimerism









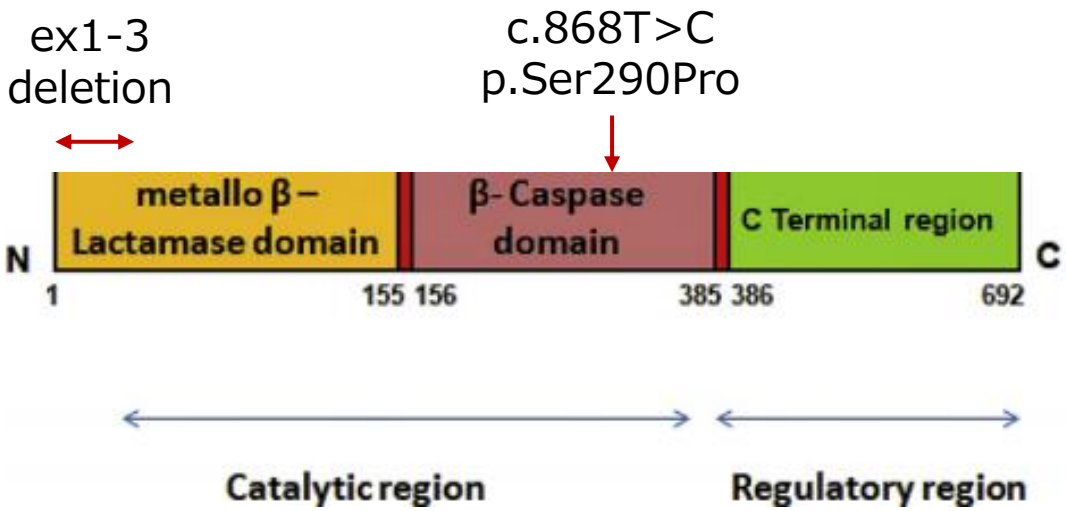


TCRαβ/CD19-depleted HSCT

A 6-month-old Korean boy

Pneumocystis pneumonia

Compound heterozygous variants in ***DCLRE1C*** gene



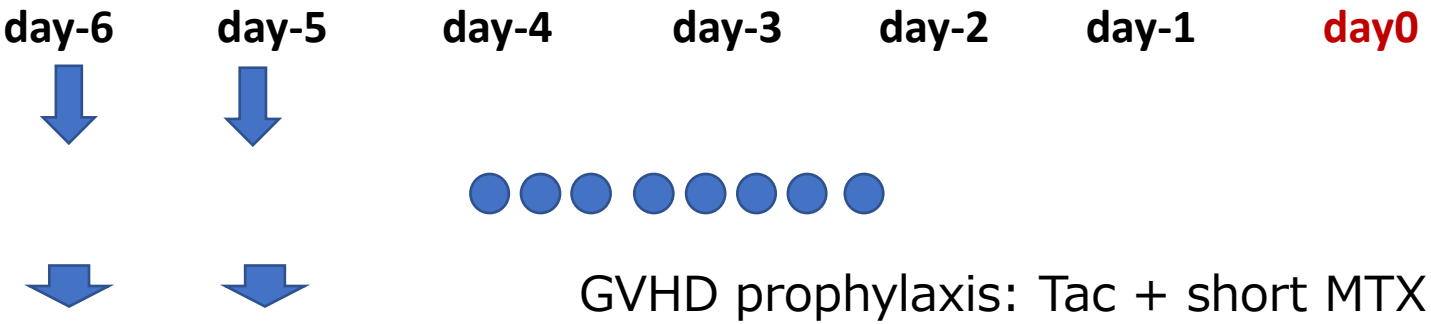
Dx: Artemis deficiency (radiation-sensitive)

→Avoid radiation and cytotoxic drug!!!

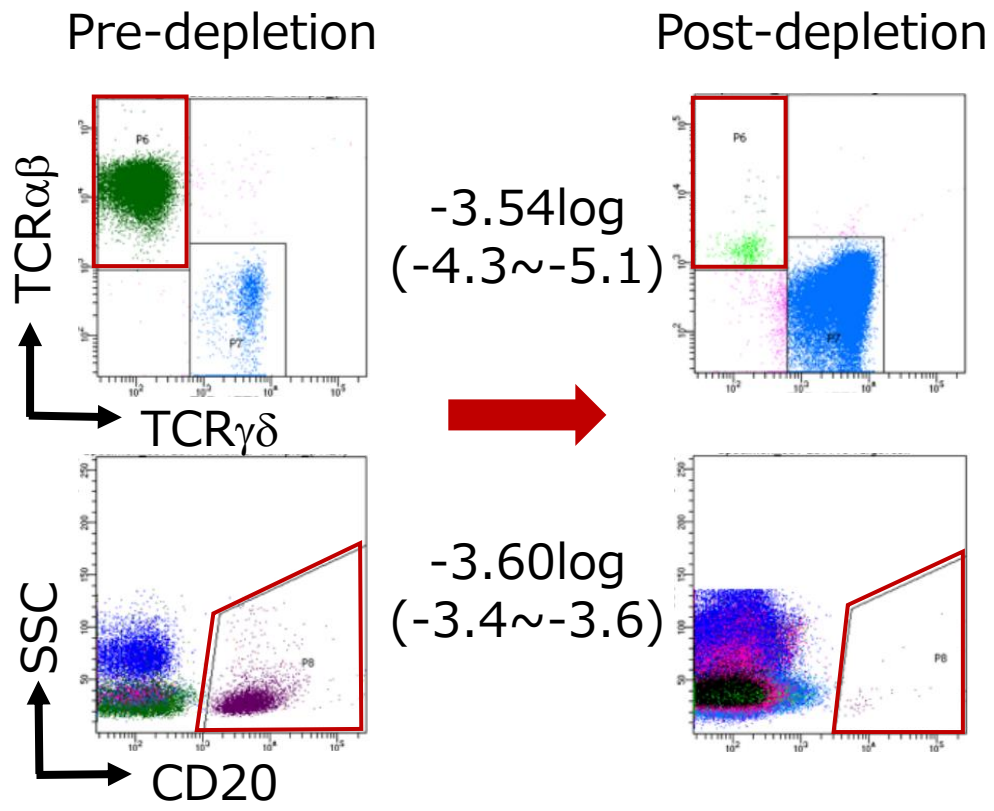
Tomomasa D. J Pediatr Hematol/Oncol (in press)

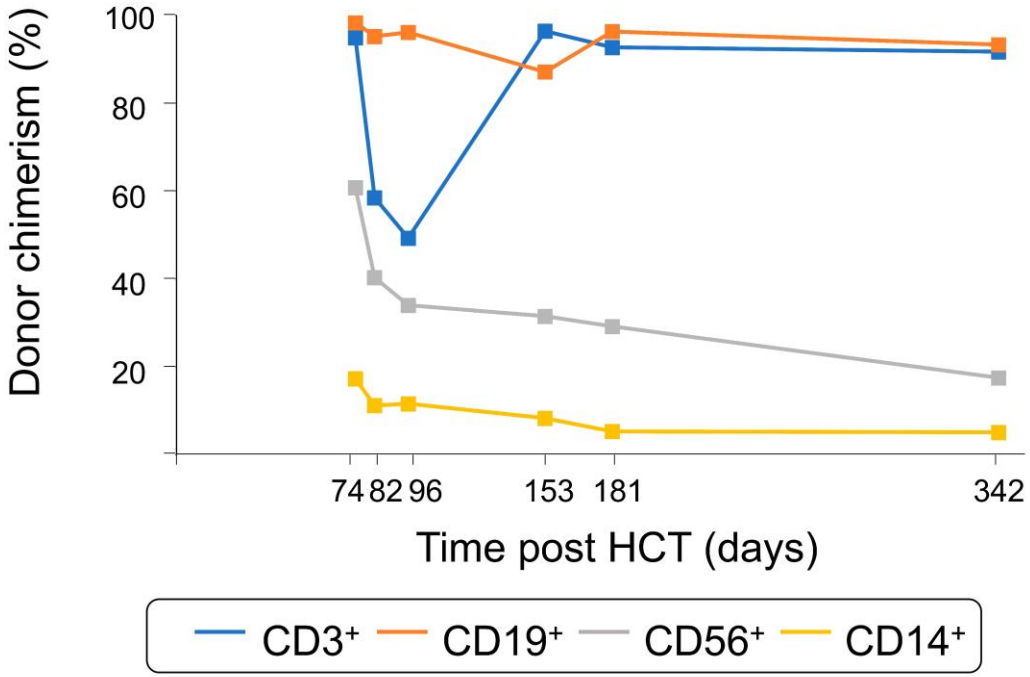
Conditioning

TT 4 mg/kg/dose
BU AUC 31.3 mg*h/L
rATG 1.25 mg/kg/dose



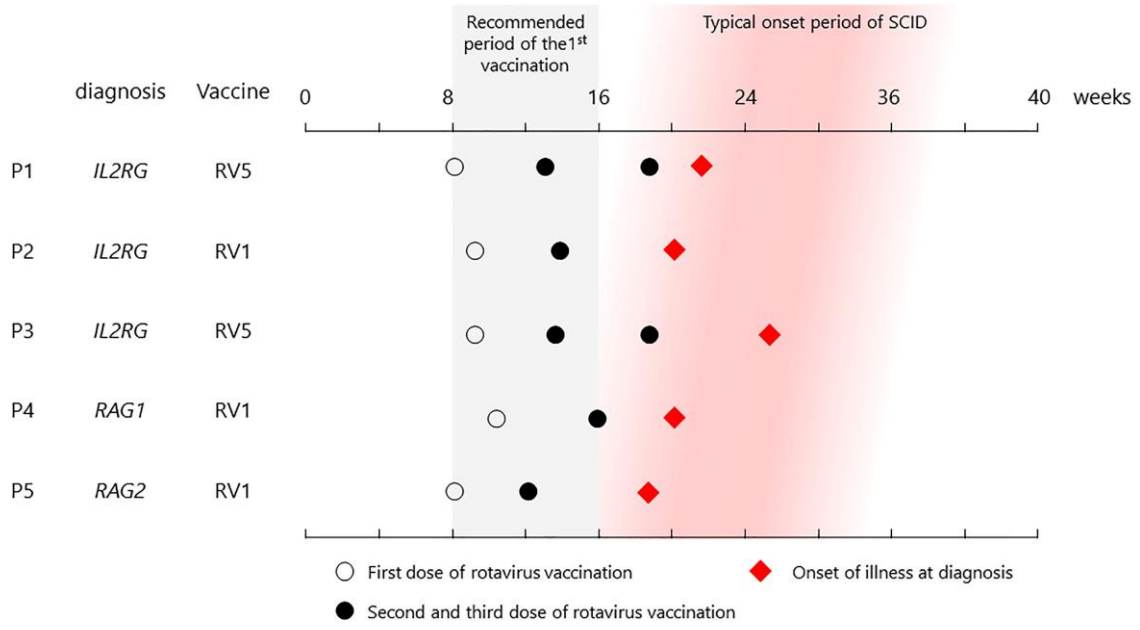
GVHD prophylaxis: Tac + short MTX



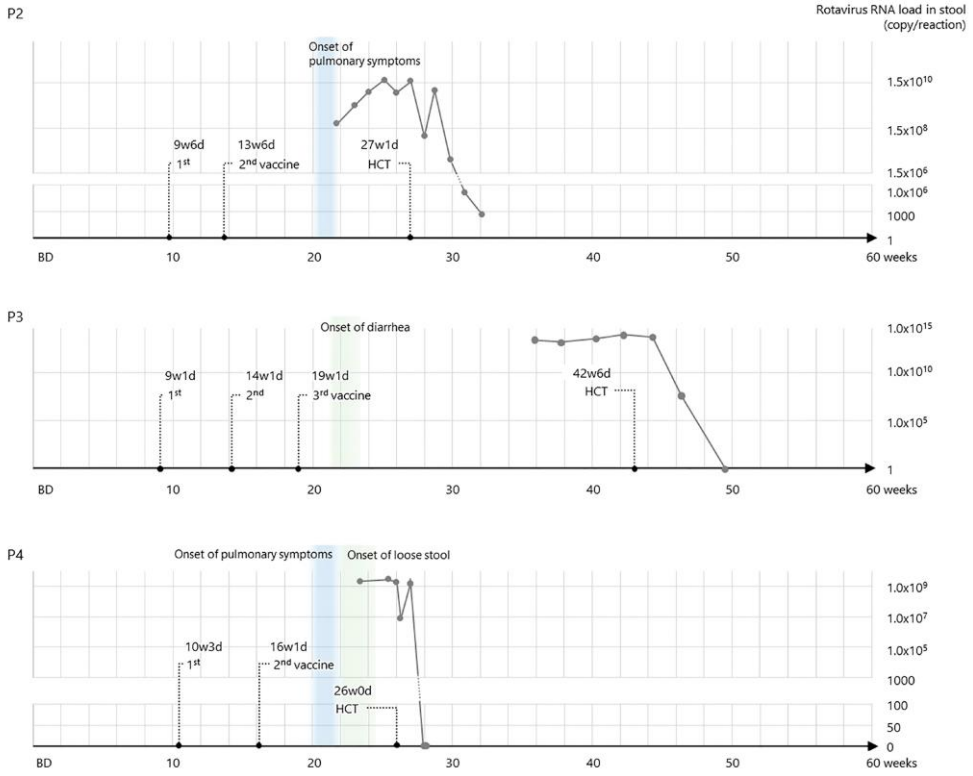


First rotavirus vaccination is given when SCID is **asymptomatic**

Tanita K, et al. Front Immunol 2022.



Diarrhea from vaccine strains



Improved by HCT

→ SCID must be diagnosed with **newborn screening** prior to rotavaccination (<8 weeks)

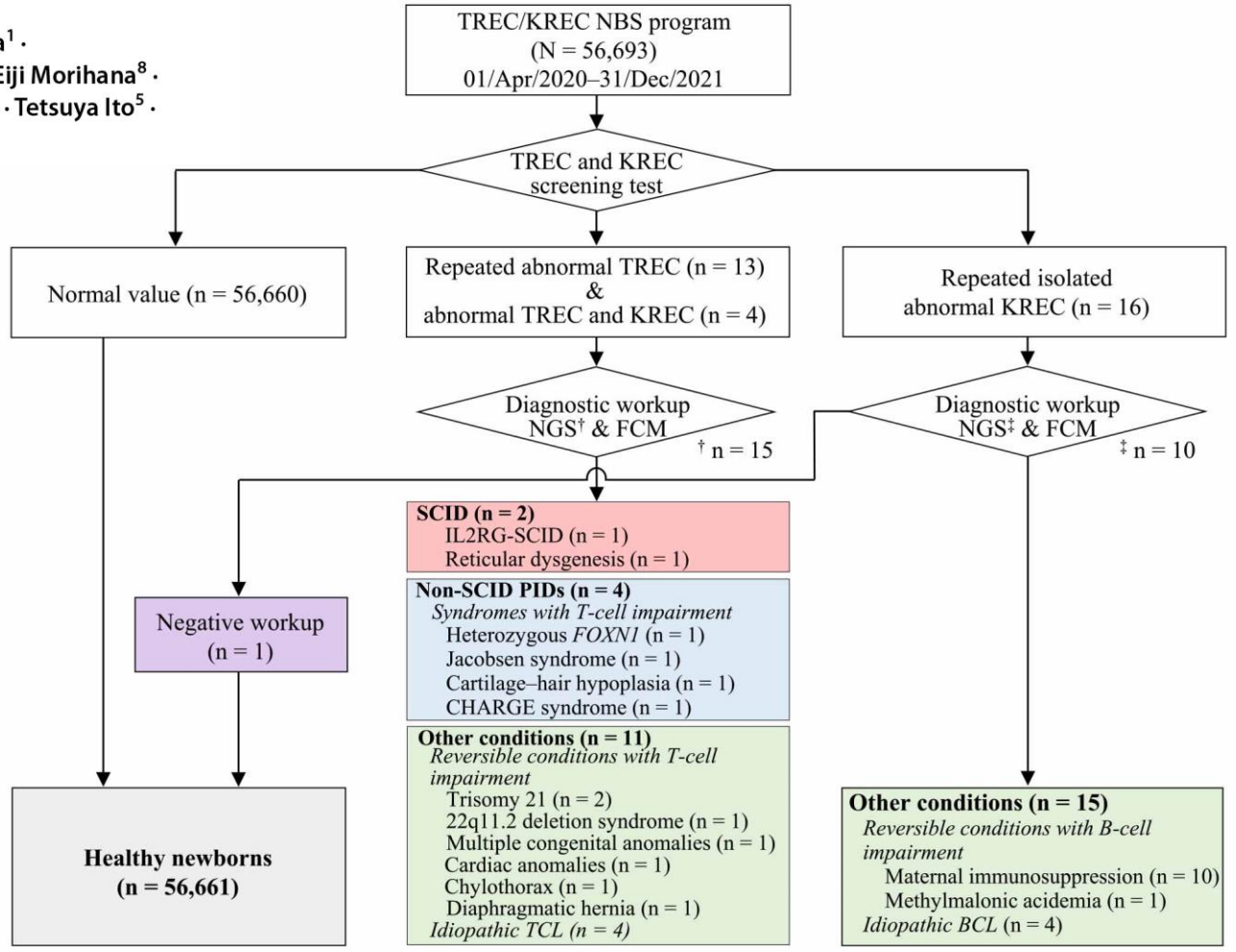
Journal of Clinical Immunology
https://doi.org/10.1007/s10875-022-01335-0

ORIGINAL ARTICLE

TREC/KREC Newborn Screening followed by Next-Generation Sequencing for Severe Combined Immunodeficiency in Japan

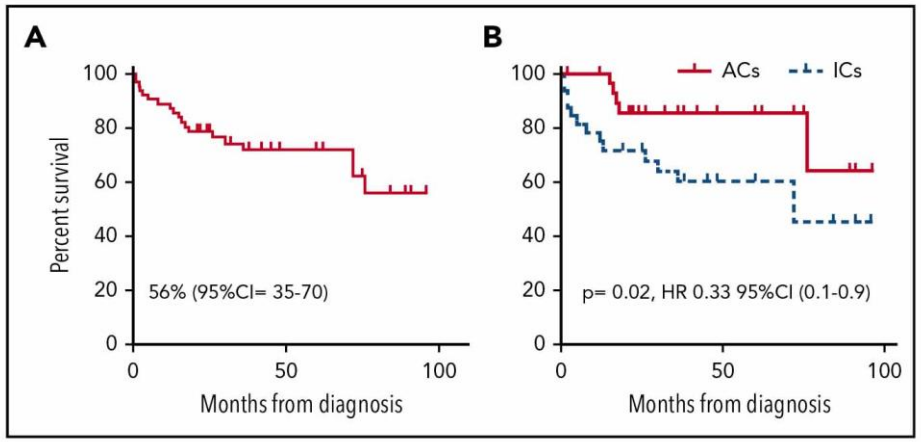
Manabu Wakamatsu[1] · Daiei Kojima[2] · Hideki Muramatsu[1] · Yusuke Okuno[3] · Shinsuke Kataoka[1] · Fumiko Nakamura[4] · Yoshimi Sakai[4] · Ikuya Tsuge[5] · Tsuyoshi Ito[6] · Kazuto Ueda[7] · Akiko Saito[7] · Eiji Morihana[8] · Yasuhiko Ito[9] · Naoki Ohashi[10] · Makito Tanaka[5] · Taihei Tanaka[11] · Seiji Kojima[1] · Yoko Nakajima[5] · Tetsuya Ito[5] · Yoshiyuki Takahashi[1]

Two patients with SCID were successfully treated with HCT



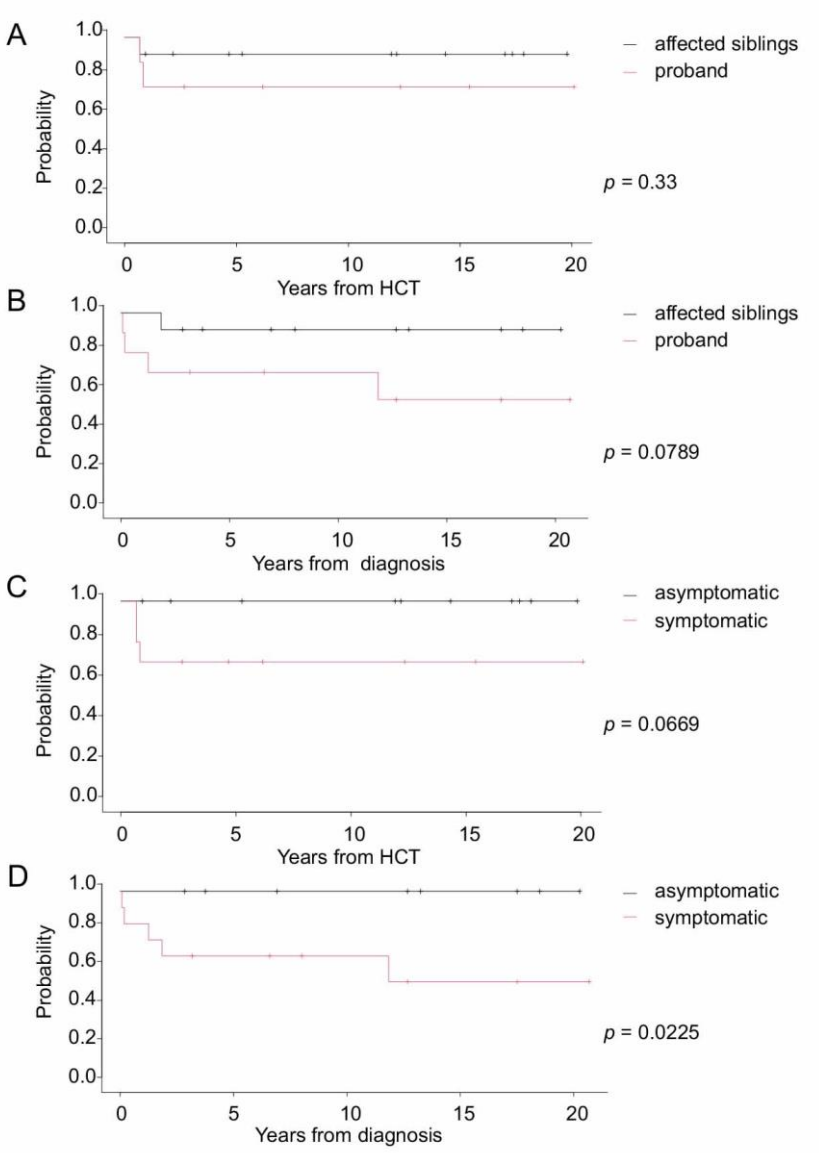
Preemptive HCT for PID

FHL syndrome



Lucchini G. Blood 2018.

XLP1



Tomomasa D. Clin Immunol 2022.

Autoinflammatory diseases are usually treated with immunosuppressants and biologics

However

Are refractory cases amenable to **HCT**?

EXPERT REVIEW OF CLINICAL IMMUNOLOGY
2022, VOL. 18, NO. 7, 667–689
https://doi.org/10.1080/1744666X.2022.2078704

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REVIEW

Hematopoietic stem cell transplantation in systemic autoinflammatory diseases - the first one hundred transplanted patients

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MVK, SIFD, HA20, PRAAS, OPACID (OAS1), DADA2, et al.

XLA patients are relatively well under Ig replacement therapy

But

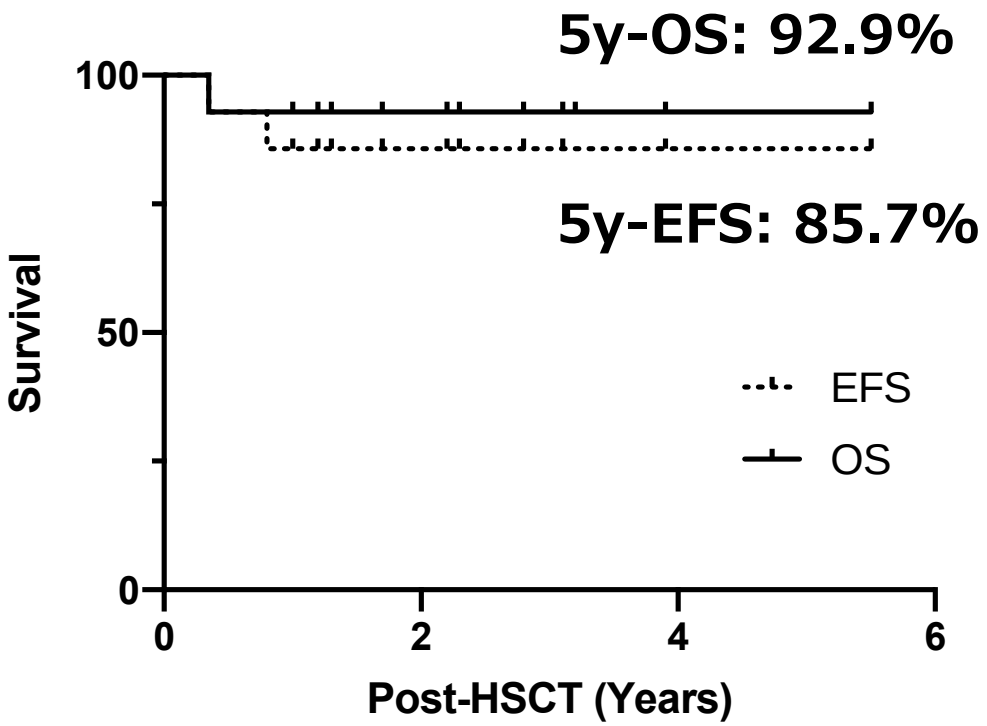
In some patients, ADL is disturbed due to severe complications

XLA can be cured by allogeneic **HCT**

Patient characteristics

		N = 14
Age at HCT (years)		10 (1.4-28)
Indication	Infection (Bacteria, Virus)	50%
	Malignancy (AML, ALL, Lymphoma)	30%
	Others (SCD, Crohn's disease)	20%
Donor source	CB	1
	PBSC	10
	BM	3
HLA matching	Matched	9
	1-locus mismatched	3
	Haploidentical	2
Conditioning regimen	MAC	4
	RIC	10
Engraftment		14 (Secondary graft failure 1)
Outcome	Alive	13 (2^{nd} transplant 1)
	Death	1 (Pneumonia)

Outcome



		n = 14
aGVHD Grade II-IV		21%
cGVHD	Limited	29%
	Extended	7%
Infection	Virus (CMV, ADV, VZV, flu)	29%
	Bacterial and Aspergillus	7%
Chimerism	Complete	86%
	High-level mixed (50-95%)	14%
Discontinuation of Ig replacement		**92%**

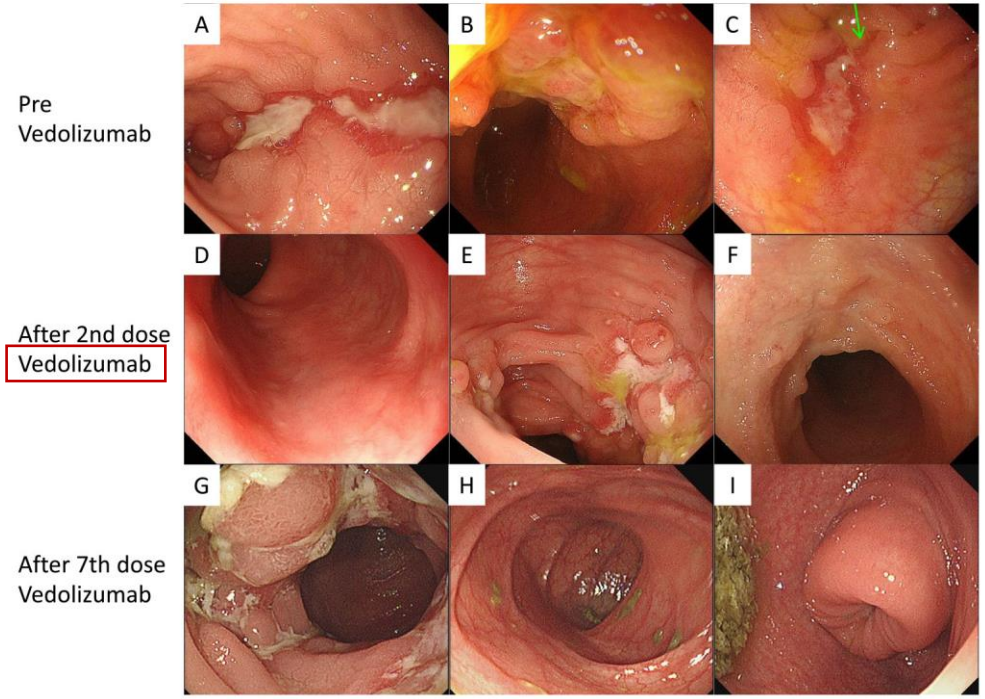
Summary (XLA-HSCT)

- High rate of engraftment and high-level donor chimerism were achieved.
- Most patients could obtain sufficient immune reconstitution and **discontinue Ig replacement**.
- HSCT may be an **effective and safe** treatment option for XLA patients with severe complications.

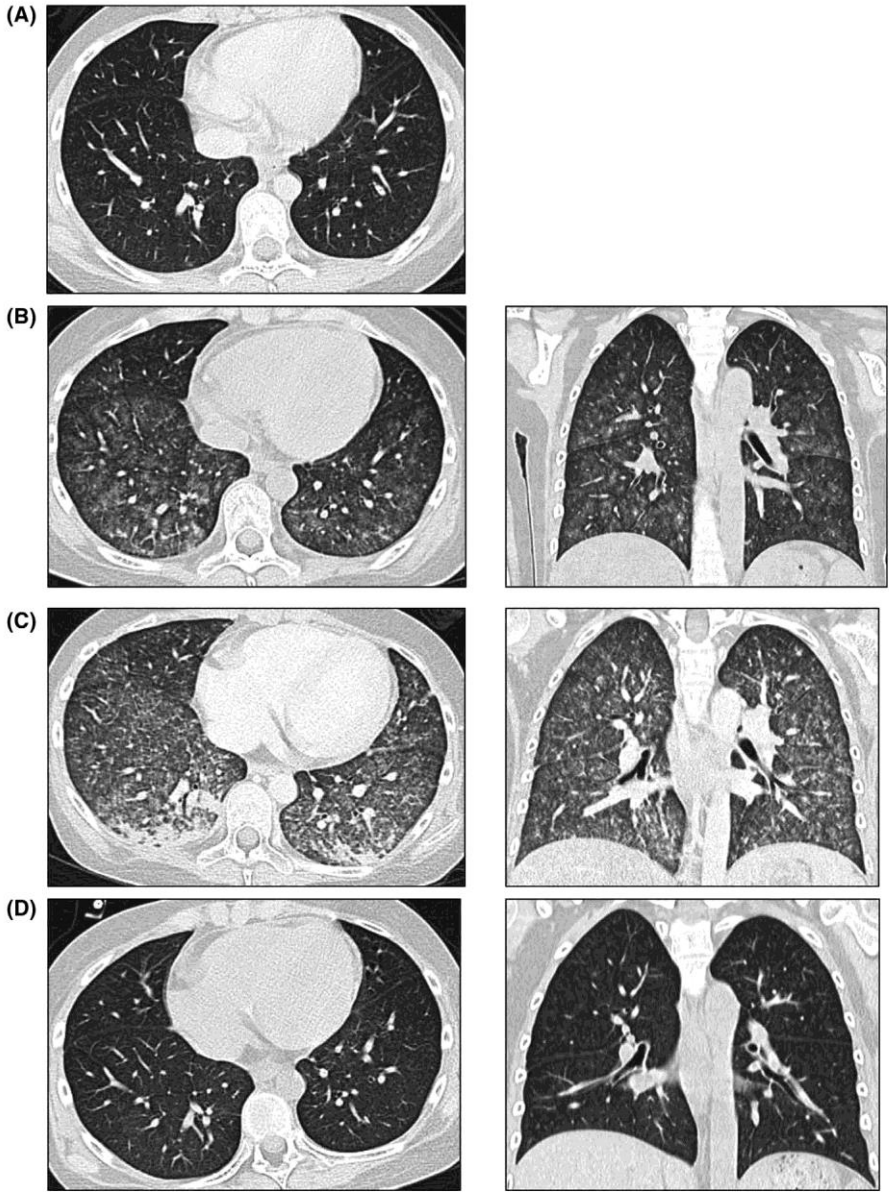
Nishimura A, Kanegane H, et al. (in preparation)

New treatment for GVHD

Steroid-refractory GI aGVHD



Isshiki K. IJH 2022.



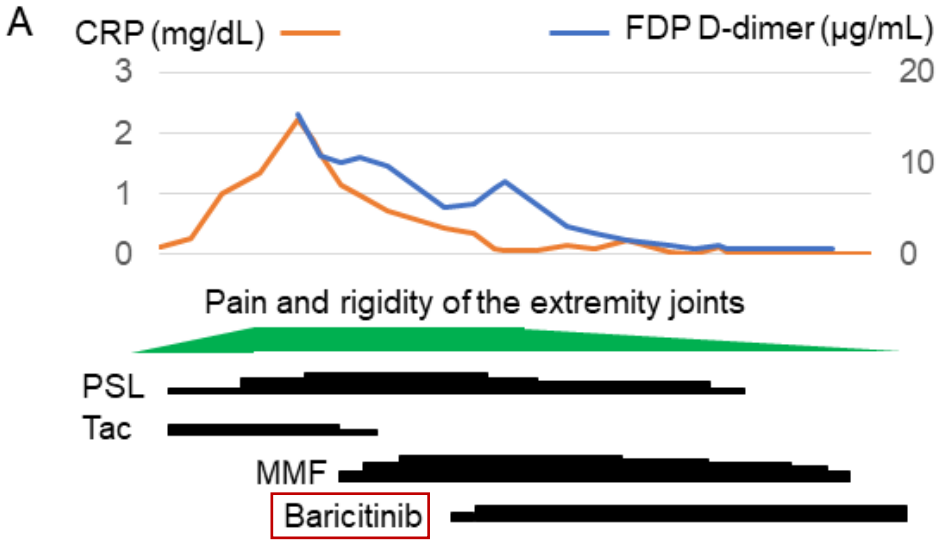
Tomomasa D. Clin Case Rep 2021.

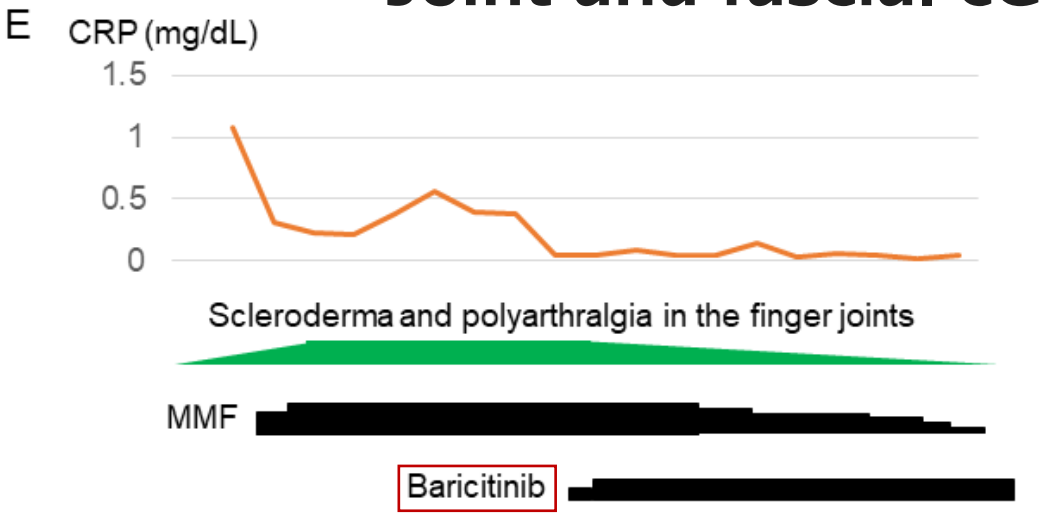
Before HCT

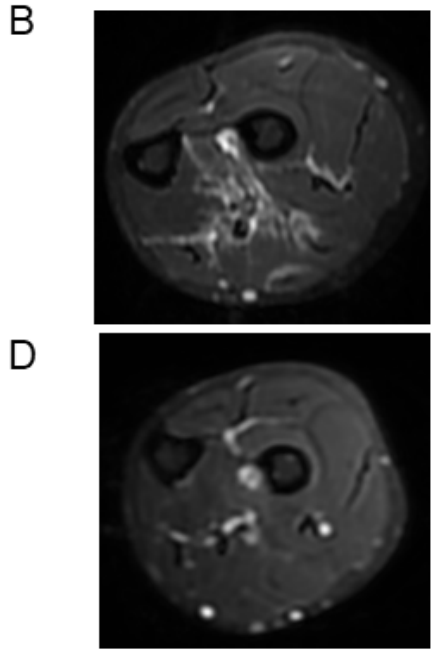
Idiopathic Pulmonary Syndrome

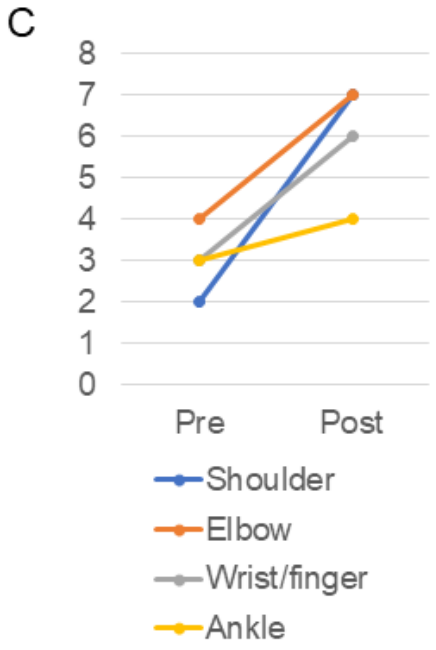
←ruxolitinib

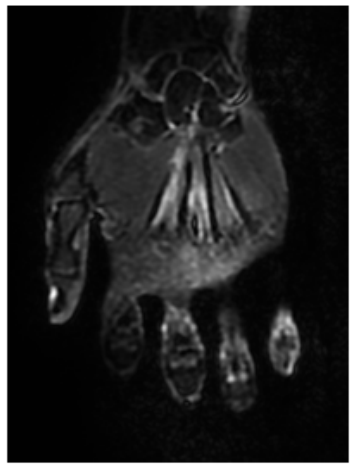
Joint and fascial cGVHD

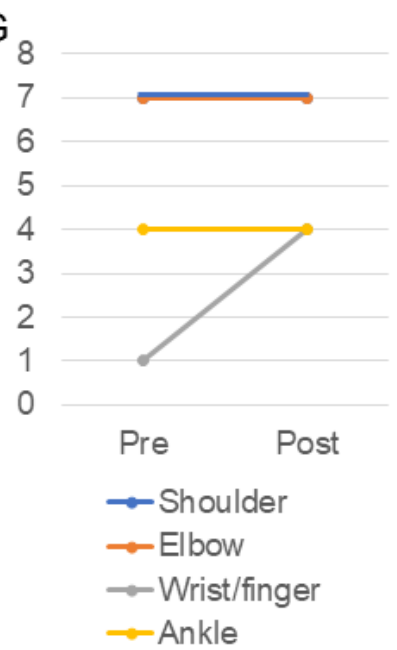












Shimizu M. Rheumatol (Oxford) 2021.

PID Tsubasa-no-kai
: PID patient organization in Japan

NPO法人
PIDつばさの会

https://npo-pidtsubasa.org/

Who we are: organized by...

- over 100 of PID patients/family
- regional medical advisors

Our mission: is to improve...

- QOL of PID patients and their family
- medical environment of PID
- public awareness of PID

PID Tsubasa-no-kai : Activity

What we do:

- publish Newsletter (almost quarterly)
- organize patients and family meetup
- organize medical lectures about PID
- organize medical Q&A session
- Lobby the government
- and so on...

The 7th Annual Scientific Meeting of the Japanese Society for Immunodeficiency and Autoinflammatory Diseases (JSIAD)
The 5th Asia-Pacific Society for Immunodeficiency (APSID) Congress

Beyond the border

Date: Fri, March 22 – Sun, March 24, 2024
Venue: Sola City Conference Center (also on Web)
4-6 Kandasurugadai, Chiyoda-ku, Tokyo, Japan

See you in Tokyo!