Donor lymphocyte infusion as a treatment of a complete DiGeorge syndrome

K.Zdráhalová[2], E.Mejstříková[1,2],T.Kalina[1,2],P.Sedláček[2], A. Janda[1], H.Žižková[3], Z.Sieglová[3],A.Šedivá[1], J.Bartůňková[1], J.Starý[2], P.Kobylka[3] , P.Hubáček [2,4], O.Hrušák[1,2]

[2]Department of Pediatric Hematology and Oncology,

[1]Department of Immunology,

[3]Institute of Hematology and Blood Transfusion,

[4]Department of Pediatrics,

Prague, Czech Republic

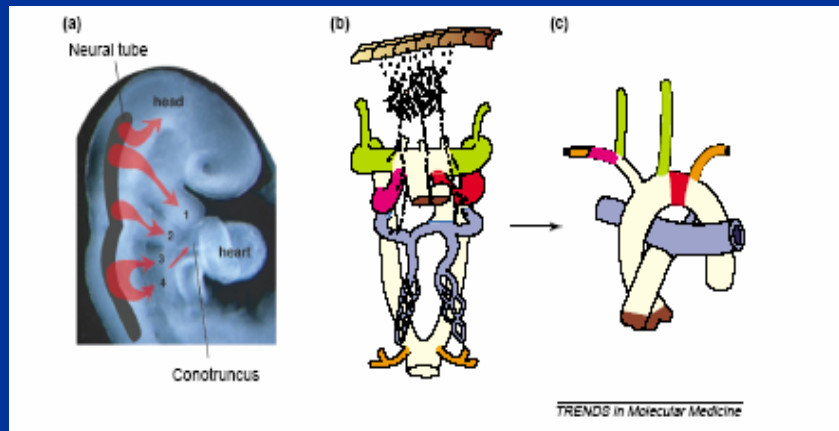
Introduction - DiGeorge syndrome

- the most common deletion syndrome in humans –
- monoallelic microdeletion of 22q11.2 (DiGeorge and velo-cardio-facial sy, conotruncal anomaly)

- variable phenotype even in pts with the same deletion

- manifestation: ("CATCH22")
- mainly heart defects; hypoparathyroidism
- thymic hypoplasia → immunodeficiency, facial dysmorphism, developmental and behavioral problems

- Deletion or interstitial deletion of 10p13 - other rare cause of DiGeorge sy (type II)



Patient: male, born June 18th 2004, now 10 months

Family history: healthy parents, 0 siblings

Personal history: 1st pregnancy, polyhydramnios → amniocentesis → normal karyotype 46, XY

term delivery, fetal hypoxia → Cesarian section, resuscitation, intubation, artificial ventilation

- esophageal atresia + tracheoesophageal fistula: D+2 operation
- bilateral choanal atresia: D+5 operation
- congenital heart defects: D+13 operation

- **Stigmatisation:**

* *face*
* *genitals*
* *eyes*
* *CNS*

- **CHARGE association**

  (Coloboma, Heart disease, Atresia choanae, Retarded growth + development and/or CNS anomalies, Genital anomalies and/or hypogonadism, Ear anomalies and/or deafness)

Problems:

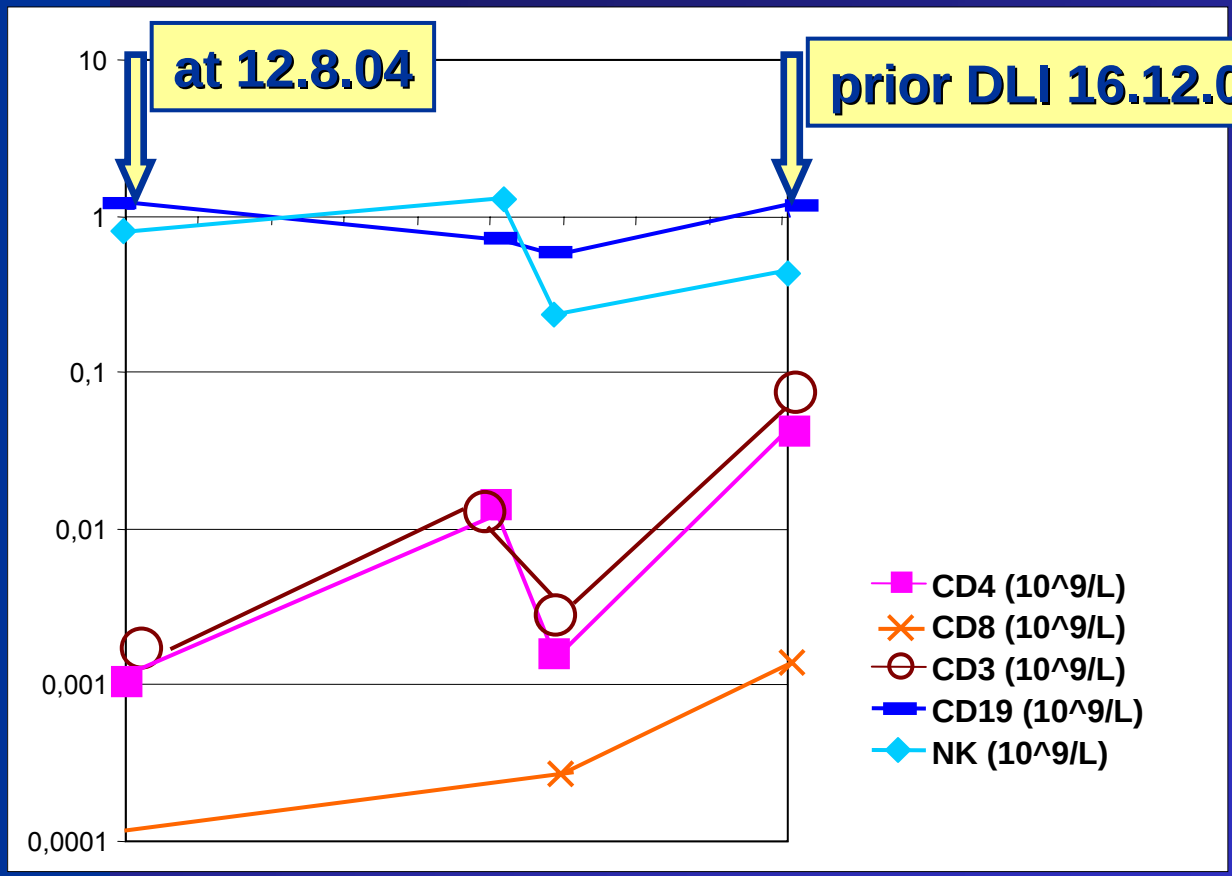
- **recurrent infections, septicemias**
- **recurrent respiratory distress → ventilation**
- **apneas, irritability, states of altered consciousness**

Immunology:

- lymphocyte subsets in 2 months of age:

CD3+	0%
NK	40%
CD4+	0%
CD8+	0%
CD19+	58%

→ absent T cells



- response to mitogens: absent
- MRI - absent thymus

Complete DiGeorge Syndrome

(diagnosis at 2 months)

- microdeletion 22q11 not found
- prophylaxis started :
  cotrimoxazole + itraconazole + IVIG

2 months of age

1st donor lymphocyte infusion

age 6 months

unrelated donor from register, 8/10 (B, Cw)

no conditioning

no GVHD prevention

1x 10^6/kg CD3+; 0.2x 10^6/kg CD34+

due to mistake non irradiated blood products administered (7 times prior 1st DLI, 1 time after 1st DLI)

1st donor lymphocyte infusion (cont.)

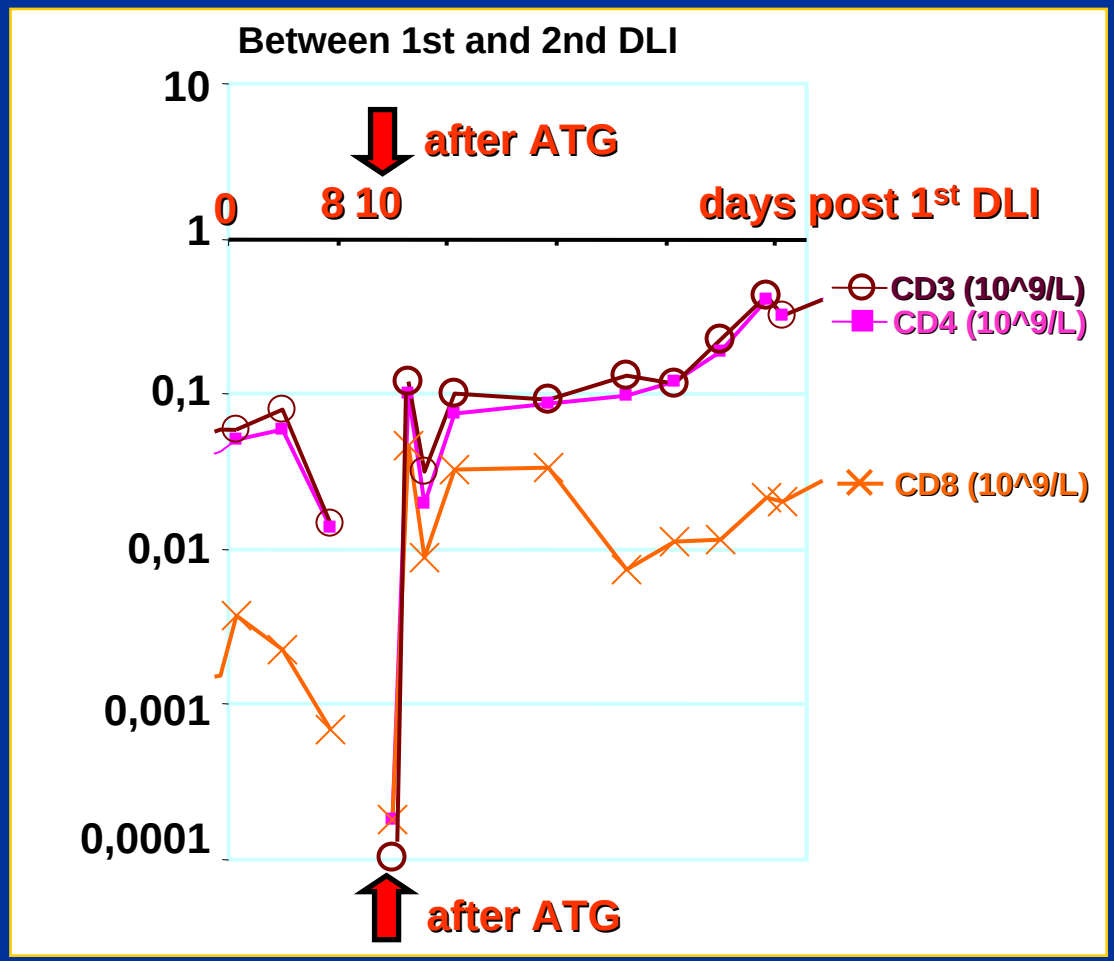
Complications:

D+10:

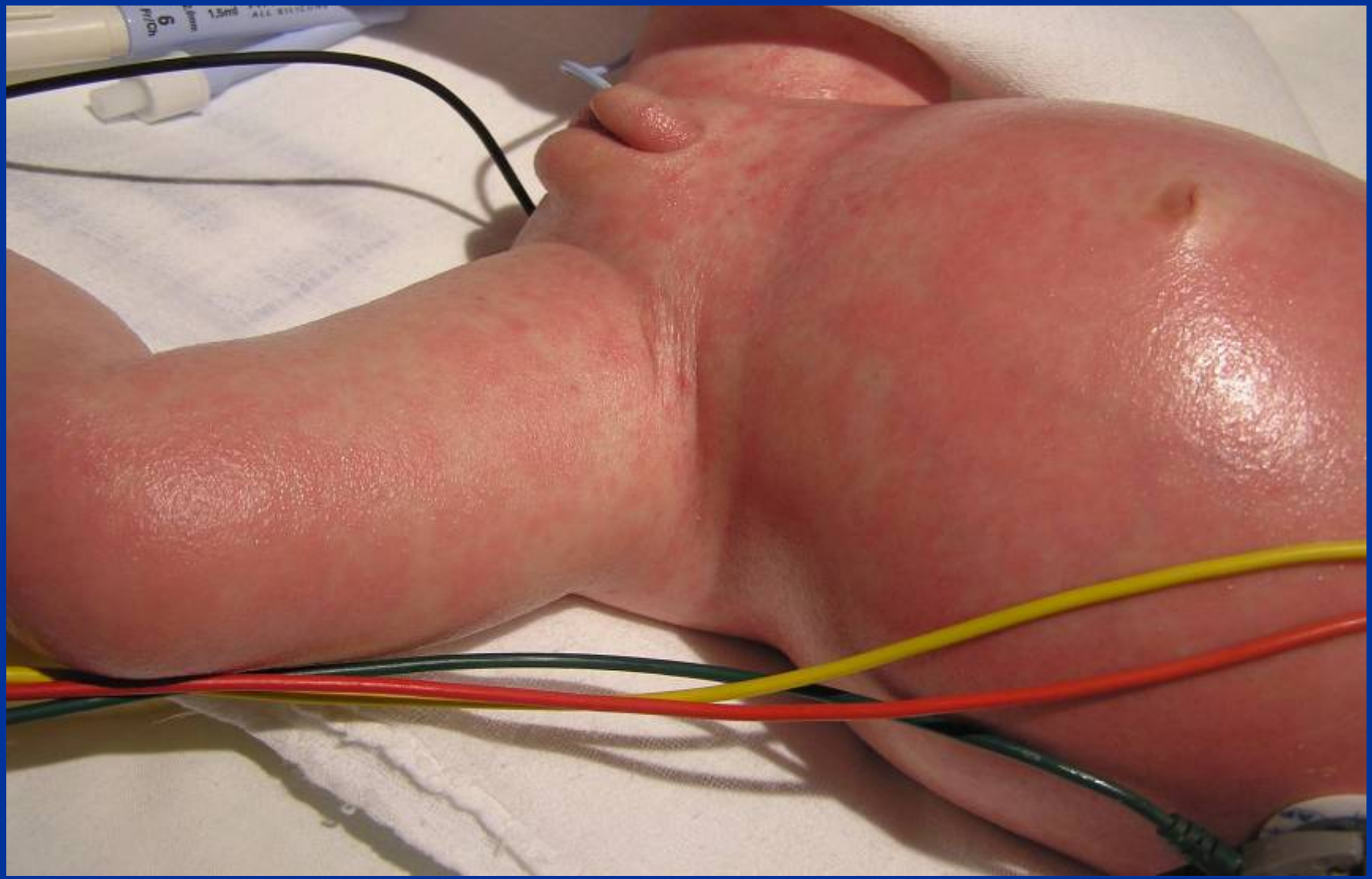
- isolated skin aGVHD (stage 3, grade II)
- sepsis
- cardiopulmonary instability
- capillary leak sy

Chimerism:

D+10 donor detected



aGVHD, Capillary leak sy



Immunosupressive therapy:

- rATG Fresenius (25mg/kg 3x D+10, D+12, D+14)
- CsA
- corticosteroids - MP (2mg/kg)

- GVHD resolved

- corticosteroids - 2 weeks 2 mg/kg, 1 week 1 mg/kg, 1 week 0.5 mg/kg, then tapered (D+35)
- CsA continued

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- D+33 last extubation! - aged 7 months

2nd donor lymphocyte infusion

age 7 months, D+36 after 1st DLI

the same donor

no conditioning

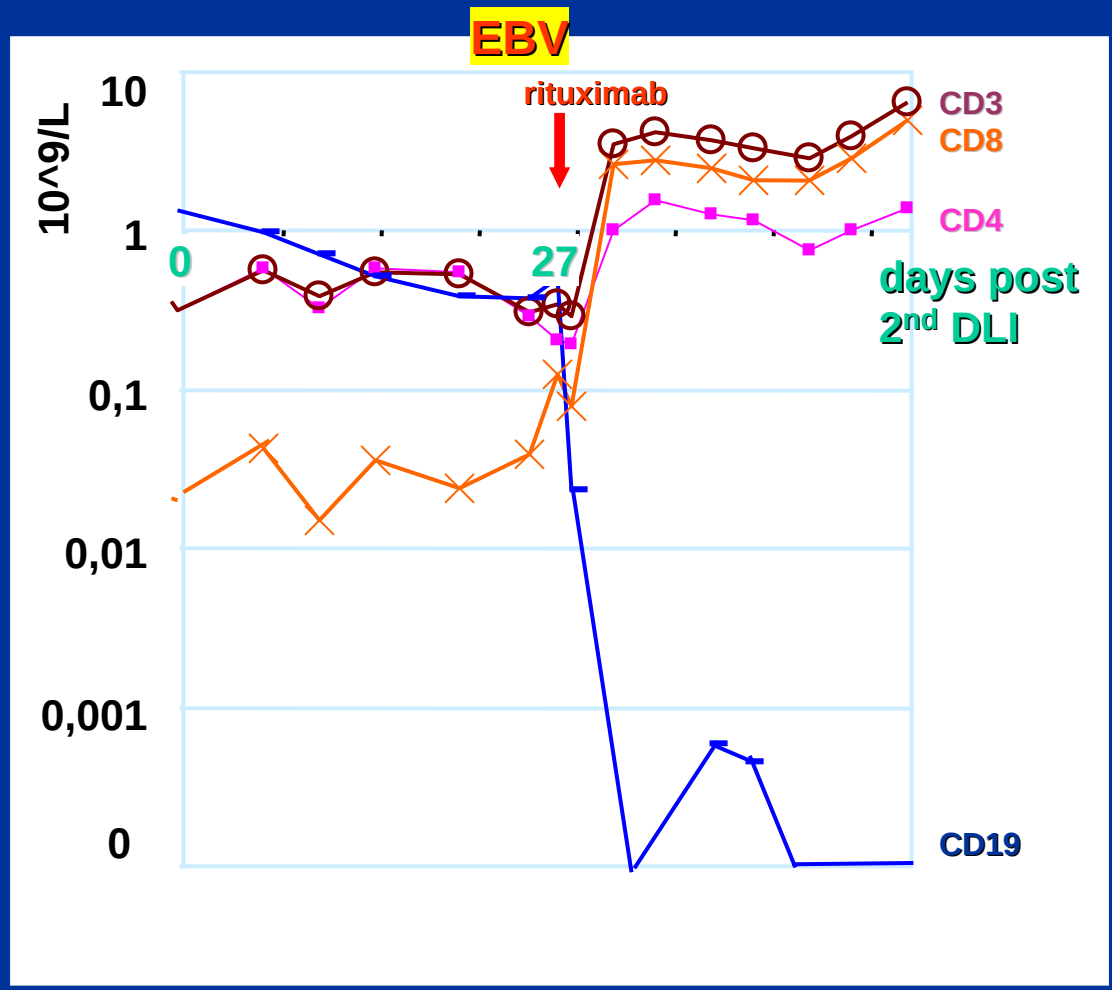
prevention of GVHD: CsA (continued)

0.89x 10^6/kg CD3+

2nd donor lymphocyte infusion (cont.)

Complications:

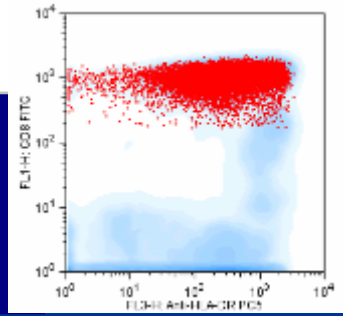
- D+27 EBV infection: (B cell proliferation, oligoclonality,↑ IgM; no clinical manifestation)
- withdrawal of CsA
- Rituximab (375 mg/m²)
- proliferation of CD8+ activated T cells started

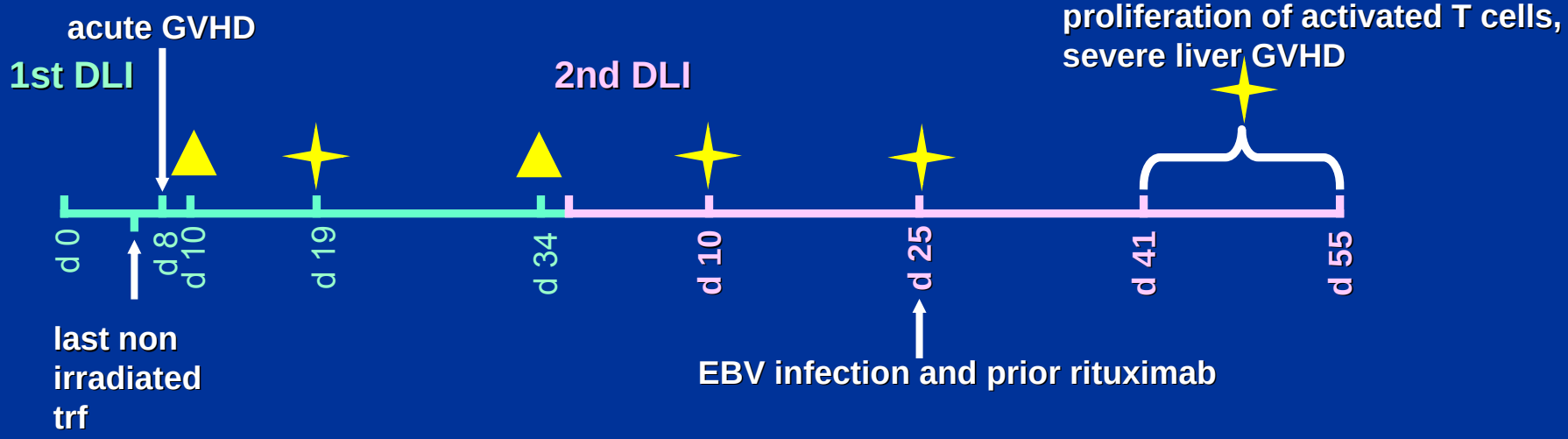


Chimerism after 1st and 2nd DLI

▲ chimerism in non separated blood: recipient mainly, donor detected

✦ chimerism in FACSorted T lymphocytes CD3+ (D+41 and D+55 CD4+ and CD8+): mainly donor





No proof of engraftment of non irradiated blood transfusions

D+34: jaundice - bilirubin 4 mg/dL

dif.dg.:

- ***hepatic GVHD***
- ***EBV lymphoproliferation*** **(EBV in blood 0; in organs?)**
- ***hepatic infection*** **- not found**

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D+35 2nd Rituximab (375 mg/m^2)

D+41 corticosteroids (MP 1 mg/kg) hepatic aGVHD
neutropenia - granulo 215!

D+55 preventive ATB, antimycotics

D+45 - D+49: agranulocytosis (0 granulo)

- ↑ corticosteroids (MP 2 mg/kg)
- CsA
- G-CSF 5x

D+52: granulo 3000

↑ bilirubin 13.7 mg/dL

→ isolated liver GVHD stage 3, grade III

D+56: rATG Fresenius 1 dose, 25mg/kg

D+57: ↑ bilirubin 23.8 mg/dL

→ isolated liver GVHD stage 4, grade IV

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- **↓ corticosteroids (D+63 1.5 mg/kg, D+83 1 mg/kg)**
- **CsA continues**

Current status:

- **D+108 after 2nd DLI, age 10 months**
- **↓ bilirubin 7.6 mg/dL**
- **CD8 activated T cells absolutely decreased**
- **slight gradual psychomotor development**

Patient aged 10 months

Thank you.