A. Introduction

Primary immunodeficiencies are rare heterogeneous disorders. Patients present with a variety of clinical symptoms and a wide range of infections and other complications. Treatment by bone marrow transplantation is increasingly successful (reference: Antoine C, Müller S, Cant AJ, et al. Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience (1968-1999) The Lancet 2003;361:553-60) and the joint EBMT / ESID Working Party has played a pivotal role designing and developing the guidelines which have led to this success.

The clinical heterogeneity of the patients, together with the fact that outcome data are based on observational studies, means that it is not yet possible to promulgate tightly defined clinical protocols for transplanting these conditions. Each case needs to be carefully evaluated in a centre which has significant ongoing experience of performing these procedures. The exact transplant protocol will be devised using these guidelines, but sometimes modified according to the particular variant of the primary immunodeficiency and / or the patient’s clinical condition. For all these reasons the Working Party strongly recommends that all patients with primary immunodeficiency are transplanted in a centre that regularly transplants such cases, and also actively participates in the Working Party, as only in this way can optimum results be obtained.

The guidelines are reviewed on an annual basis and sub-groups of Working Party members revise some of the guidelines for specific conditions each year. The names of these people are given alongside each guideline to facilitate communication and discussion.

B. Conditioning Regimen

In almost all the condition regimen used in inherited diseases, three drugs are utilised on different dosage, combinations and on different time schedules, according to the type of disease and the age of patients.

Moreover, we have summarised here below the most frequent used dosages.

**Oral Busulfan**:

Either: Myleran oral  
< 5yr 5,0mg/kg/day in 4doses (TD* 20,0mg/kg)  
> 5yr 4,0mg/kg/day in 4doses (TD 16,0mg/kg)

Or: Busulfex i.v.  
≤ 5 yr 4mg/kg/dayx 4 (TD : 16mg/kg)  
> 5 yr 3,2mg/kg/dayx4 (TD : 12mg/kg)

**Cyclophosphamide**  
50mg/kg/day x 4 (TD 200 mg/kg)

**Fludarabine**  
40mg/m²/day x 4 (TD 160mg/m²)

**RABBIT ATG**  
2,5mg/kg/day x 4 (TD 10mg/kg)

**Campath**  

* TD : Total dose
A/ Guidelines for BMT in Chronic Granulomatous Disease (CGD)

Revision and studied by Reinhard Seger and Terry Flood

EBMT/ESID WP Inborn Errors: Guidelines for BMT in CGD

A1. Indications

X-CGD or a/r-CGD with HLA-(geno)identical donor plus one of the following:

- Non-availability of specialist medical care
- Non-compliance with long-term antibiotic/antimycotic prophylaxis
- ≥ 1 life-threatening infection in the past
- Severe granulomatous disease with progressive organ dysfunction (e.g. lung restriction)
- Steroid-dependent granulomatous disease (e.g. colitis)
- Ongoing therapy-refractory infection (e.g. aspergillosis)

(N.B. Uncomplicated CGD is not an indication)

A2. Pre- and post-transplant work-up

2.1. Immunologic

- Quantitative measurement of respiratory burst
- Cytochemical NBT-test of maternal cells and of donor cells (mosaicism in X-CGD)
- Surface gp91phox expression
- Immunoblot (gp91, p22, p47, p67phox)
- Mutation analysis (if gp91 or p22phox def. suspected)

2.2. Pulmonary

- Chest x-ray and CT, O₂-saturation, lung-function,
- If pulmonary infection/inflammation:
  CT, PET or PET/CT-scan, bronchoscopy + lavage ± lungbiopsy and cultures

2.3. Gastrointestinal

- Weight/length curves, malabsorption parameters
- If colitis:
  Abdominal contrast-CT, colonoscopy, colonic biopsy and cultures

A3. Conditioning for HLA-genoid sibling donor

3.1. Standard patient: Myeloablative

- Busulfan (day -9 to day -6): Dosage to be adjusted depending on levels
  
  Either: Myleran oral < 5yr 5,0mg/kg/day in 4doses (TD 20,0mg/kg)
  > 5yr 4,0mg/kg/day in 4doses (TD 16,0mg/kg)

  Or: Busulfex iv According to local (study) guidelines

- Cyclophosphamide (days -5 to -2) 50mg/kg/day (TD 200mg/kg)
- GvHD-prophylaxis:
CsA (from day -1)  
MTX (days +1, +3, +6, +11) 10 mg/ m²/day (TD 40mg/m²) not “fat”  
In vitro T-cell-depletion No “fat”

3.2. **High risk patient (with active/chronic infection/inflammation): Myeloablative**  
Same as 3.1., plus:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campath 1H (day -4 to -2)</td>
<td>0,1mg/kg/day (TD 0,3mg/kg)</td>
</tr>
<tr>
<td>MTX</td>
<td>No not “fat”</td>
</tr>
</tbody>
</table>

A4. **Conditioning for HLA 10/10 phenoid. MUD or related donor**  
(Still experimental and very risky)

4.1. **Standard patient:** Myeloablative  
Same as 3.1.1. plus

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campath 1H (day -8 to -4)</td>
<td>0,2mg/kg/day (TD 1mg/kg)</td>
</tr>
<tr>
<td>MTX (day +3 and +11)</td>
<td>10mg/m²/day (TD 20mg/m²)</td>
</tr>
</tbody>
</table>

4.2. **High risk patient:** Myelosuppressive

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine (days -7 to -3)</td>
<td>30mg/m²/day (TD 150mg/m²)</td>
</tr>
<tr>
<td>Melphalane (day -2)</td>
<td>140mg/m²</td>
</tr>
<tr>
<td>Campath 1H (days -8 to -4)</td>
<td>0,2mg/kg/day (TD 1mg/kg)</td>
</tr>
<tr>
<td>CsA (from day -1)</td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>No</td>
</tr>
<tr>
<td>In vitro T-cell depletion</td>
<td>No</td>
</tr>
</tbody>
</table>

A5. **Supportive therapy**

5.1 **Pre-transplant**  
Optimal reduction of infectious/inflammatory foci by antibiotics/antimycotics, and if necessary by tranfusions of leukocytes from unrelated donors (G-CSF-induced if possible), surgery, steroids.

5.2 **Post-transplant**

5.2.1. **Antimycotics**  
If aspergillosis in the past:

administer iv Ambisome or Voriconazole alone (dosage see below)

If ongoing florid aspergillosis, treat with
Either: Ambisome 3-5 mg/kg/day
   + Caspofungin  + 1 mg/kg/day
Or: Voriconazole 8 mg/kg/day in 2x
   + Caspofungin  + 1 mg/kg/day in 1x not “fat”
(adjust CsA-levels!)

5.2.2. Leukocyte transfusions
If florid infection: Transfuse leukocytes every 2 days during aplasia.
Administer G-CSF to patient from day +7 till neutrophil take (10 µg/kg/day).

5.2.3. Antiinflammatory treatment
If active inflammation: At neutrophil take stop leukocyte transfusions and G-CSF,
consider Steroids 1mg/kg/day for 1 week, then taper according to response.

5.2.4. GvHD treatment
If acute GvHD: aggressive treatment on case by case basis.
At first signs: steroids 5mg/kg/day.
If no response: Consider other modalities including further Campath 1H.

5.2.5. Antiinfectious prophylaxis
Campath 1H will lead to a moderate delay of T-cell-reconstitution. Continue oral
Acyclovir/septrin/itraconazole prophylaxis till CD4 counts are over 300/ul.

A6. Reporting
Please report your transplant to the Immunodeficiency registry in Paris (P. Landais,
landais@necker.fr) using the general form and in addition to the CGD registry in
Zurich/Newcastle (R.Seger/T.Flood, reinhard.seger@kispi.unizh.ch) using the CGD-specific
form.

A7. Reasoning behind protocol
BMT for CGD with active/chronic infection/inflammation is characterized by a high risk of
microbial dissemination early in aplasia, and by severe GvHD and inflammatory flare-up (1).
The latter two are presumably caused by high and persisting chemokine levels in CGD recipients
and influx of alloreactive donor T-cells and monocytes into infected/inflamed organs (2).
Campath 1H would partially inactivate/deplete these cells in vivo (without running the risk of
EBV lymphoproliferative disease as seen with ALG). Total in vitro T-cell depletion in the
HLA id setting (3) is explicitly avoided by our working party in order not to endanger stem cell
engraftment. HLA non identical grafts are presently disadvised.

A8. Literature:
1. R. Seger et al: Treatment of CGD with myeloablative conditioning and an unmodified
   allograft. Blood, 2002, 100, 4344-4350
2. S. Yang et al: Exuberant inflammation in nicotinamide adenine dinucleotide phosphate-
   oxidase-deficient mice after allogeneic marrow transplantation. J. Immunol. 2002, 168, 5840 -
   5847
3. ME. Horwitz et al: Treatment of CGD with nonmyeloablative conditioning and T-cell-
If you should face adverse events, please inform as soon as possible the coordinator of this study:

- **Reinhard Seger** (Universitats Kinderspital – Zurich – Switzerland) tel: 41.1.2667311 / fax: 41.1.2667171 / Email: reinhard.seger@kispi.unizh.ch
- **Terry Flood** (Newcastle General Hospital – United Kingdom) tel: 44.191.2738811 / fax: 44.191.2730183 / Email: terence.flood@ncl.ac.uk
B/ BMT for CD40 Ligand Deficiency Guidelines

Revision and studied by Graham Davies and Andy Gennery

B1. Optimal management of newly diagnosed cases
   . PCP prophylaxis
   . Adequate IVIG replacement
   . Cryptosporidium avoidance
     - Boiled / filtered water
     - +/- Antimicrobial Prophylaxis
   . Monitoring for organ disease
     . Tissue Typing

B2. Monitoring for liver disease
   . Regular measurements of transaminases + Gamma GT
   . Ultrasound scan at least 1/year
   . Stool for Cryptosporidium
   . If abnormal biochemistry or ultrasound need :
     - Liver biopsy
     - ERCP

B3. When to do BMT ?
Depends on type of donor available
   . Matched Sibling Donor
     - At diagnosis (and without complications)
   . Matched Unrelated Donor
     - Possibly at diagnosis
     - Definitely if early complications detected
   . Mis-matched Unrelated Donor
     - Only at stage of established early complications
   . Mismatched Related (Haplo)
     - There is no experience of these
     - Consider if progressive organ damage

B4. Conditioning
   . No Organ Damage
     - Busulphan & Cyclophosphamide
     OR Fludarabine/Melphalan / ATG or Aletuzemab (Reduced intensity conditioning)
   . Established Organ Damage (usually involving Lungs and/or Liver)
     - Reduced intensity conditioning

B5. T cell Depletion
   . Has been used successfully in a number of cases
     . However, avoid if possible (risk of uncontrolled Cryptosporidial disease)
     . Consider using allo-depleted T cells – particularly if haplo-identical BMT being attempted

B6. Cryptosporidial Prophylaxis during BMT
   . No evidence for efficacy in BMT
   . Three possible drugs
     - Azithromycin, Nitazoxa
     - Paromomycin
- Potentially ototoxic
- May be absorbed from GI tract if mucositis occurs
  - Azithromycin & Nitazoxanide have low toxicity – may get some disturbance of transaminases with the latter
  
  - Propose:
    - CP negative cases (PCR neg) use Azithromycin alone
    - CP positive (or + history) cases use Azithromycin + 1 other drug
    - Add third drug if overt Cryptosporidial disease occurs

**B7. Complications meriting consideration of transplantation**

- Histological or radiological abnormalities of liver
- Lung damage – early brochiectasis
- Enteropathy
- Neutropenia not responsive to increased dosing with IVIG
- Persistent Cryptosporidium excretion
- Infection with Toxoplasma

If you should face adverse events, please inform as soon as possible the coordinator of this study:

**Graham Davies** *(Hospital for Children NHS Trust – United Kingdom) Tel: 44.207.8138403 – Fax: 44.207.813.8552 – Email: daviegl@gosh.nhs.uk*

**Andrew R Gennery** *(Newcastle General Hospital – United Kingdom) Tel: 44.191.2732211 – Fax: 44.191.2730861 – Email: A.R.Gennery@ncl.ac.uk*
C/ Severe Combined Immunodeficiency (SCID)

Revision and studied by Wilhelm Friedrich

**C1. genotypically identical donor** *
(including 1 antigen (A or B) mismatched, but otherwise genotypically identical donor)

- conditioning: no
- T-cell depletion: no
- GvHD prophylaxis: no
- exception: 1 antigen mismatched donor: CsA

(* applies also for ADA-, Omenn S. and other “leaky” SCID, SCID with circulating maternal GvHD)

**C2. matched unrelated donor (MUD)**
**phenotypically identical family donor:**

- Busulfan: (day -10 to day -7)
  - oral: 4 mg/kg/day x 4 (total: 16 mg/kg)
  - i.v.: 3.2 mg/kg/day x 4 (total: 12.8 mg/kg)

Cyclophosphamide (day -5 to -2) 50 mg/kg/day x 4 (total: 200 mg/kg)
- ATG: yes
- CsA: yes

**C3. HLA- nonidentical (haplo) family donor**

- Busulfan: (day -10 to day -7)
  - oral: 4 mg/kg/day x 4 (total: 16 mg/kg)
  - IV: 3.2 mg/kg/day x 4 (total: 12.8 mg/kg)

Cyclophosphamide: (day -5 to -2) 50 mg/kg/day x 4 (total: 200 mg/kg)
- T cell depletion by CD34 + selection: yes
- CsA: no

(in case of primary GvHD from maternal-fetal transfusion or Omenn Syndrome, therapy / prophylaxis of GvHD is usually needed and should be continued for 3 months)

**if clinical status unstable (serious respiratory problems)**

- use mother as donor
- T-cell depletion: yes
- CsA: no

in ADA deficiency:
- PEG-ADA is an option
If you should face adverse events, please inform as soon as possible the coordinator of this study:

**Wilhelm Friedrich** *(University of Ulm – Germany)* Tel: 49.731.5024685 – Email: *Wilhelm.friedrich@medizin.uni-ulm.de*
D/ Wiskott-Aldrich Syndrome (WAS)  
Combined Immunodeficiency (CID)  
Leukocyte Adhesion Deficiency (LAD)  
Purine Nucleoside Phosphorylase Deficiency (PNP)

Revision and studied by Wilhelm Friedrich

D1. __genotypically identical donor__

- **Busulfan** (day -10 to day -7) See Section B
- Cyclophosphamide (day -5 to -2) See Section B
- T-cell depletion: no
- ATG: no
- CsA: yes
- MTX: no

D2. matched unrelated donor (MUD)  
phenotype identical related donor:

Option 1: __No T cell depletion__

- Busulfan / Busulfex (See Section B)
- Cyclophosphamide (See Section B)
- ATG: yes
- T-cell depletion: optional

if no T-cell depletion:
- CsA: yes
- MTX: yes

Option 2: __T cell depletion__

- Busulfan: See Section B
- Fludarabine (See Section B and foot note)*
- **Cyclophosphamide  2 x 60 mg/kg (total 120 mg/kg)**
- Rabbit ATG (Sangstat) 4x2.5 mg/kg (total 10 mg/kg)
- CSA: No
- MTX: No

* except CID patients
Option 3: Reduced intensity protocol – See section H

D3. HLA-nonidentical (haplo) family donor

- Busulfan /Busulfex (see Section B)
- Cyclophosphamide (see Section B)
- Fludarabine (see 2.2 – Section B)
- ATG: yes
- T-cell depletion: yes
- CsA: no
- MTX: no
E/ Osteopetrosis

Revision and studied by Colin Steward

There have been promising results in recent years with the use of mismatched family donors, i.e. mismatched for 1-5 of 10 antigens tested. If a genotypically identical donor is not available and the patient has a severe phenotype (with existing or incipient visual loss) a mismatched family donor allows rapid transplantation. Use of mismatched unrelated donors is not recommended.

Notes:

. Carbonic anhydrase type II deficiency causes milder OP but with CNS involvement. It is unclear that the latter responds to transplantation. Exclude this deficiency and discuss with experts if found.

. Transient cases of osteosclerosis are well described. In less severely affected infants repeat X-ray and comparison with original films is recommended just before commencing conditioning therapy.

. Children may be irritable due to fractures (common) or hydrocephalus (rarer). The commonest cause of severe irritability is neuronopathic osteopetrosis, a metabolic disease causing early CNS deterioration and characterised by CNS inclusions as seen in ceroid lipofuscinosis. Children may exhibit spasticity, retinal changes, cerebral atrophy and agenesis of corpus callosum.

. Among children with severe OP, 50% of patients will have ATP6i (proton pump) mutations. Others may have mutations of GL (grey lethal) or CLCN7 (chloride channel) genes.

E1. genotypically identical donor:
same as Section D1

E2. matched unrelated donor (MUD):
same as Section D2

E3. HLA-nonidentical family donor:

- Busulfan (day -13 to day -10) : For the dosage see Section B – Page 1
- Fludarabine: (day -9 to day -6) : See Section B for the dosage
- Cyclophosphamide : (day -5 to -2) See Section B for the dosage
- RABBIT ATG: yes
- T-cell depletion: yes
- CsA: no

HLA class II deficiency : same protocol as osteopetrosis

If you should face adverse events, please inform as soon as possible the coordinator of this study:

Colin Steward (Royal hospital for children – United Kingdom) Email : colin.steward@bristol.ac.uk
F/ HLA Class II deficiency : same protocol as osteopetrosis

G/ Hemophagocytic Lymphohistiocytosis
Chediak-Higashi Syndrome
Griscelli Syndrome

G1. genotypical identical donor
matched unrelated donor (MUD)
phenotype identical related donor

- Rabbit ATG day -14 to -10 (dose: 5mg / kg/ day x 5)
- Busulfan (day -10 to day -7) See Section B page 1
- Cyclophosphamide : (day -5 to -2) : See Section B page 1
- T-cell depletion: no
- CsA: yes
- MTX: yes

G2. HLA – non identical family donor

- Rabbit ATG day -14 to -10 (dose: 5mg / kg/ day x 5)
- Busulfan (day -10 to day -7) See Section B
- Cyclophosphamide : (day -5 to -2) See Section B
- T-cell depletion: yes
- CsA: no
- MTX: no

H/ Reduced Intensity Guideline for 10/10 or 9/10 Unrelated Donor Transplant for Non-SCID Immunodeficiency

Revision and studied by Paul Veys

Monitoring
- Weekly CMV, EBV & Adenovirus blood PCR. Weekly urine DEAFF for CMV

Prophylactic medication
- Itraconazole syrup: 5mg/kg po od, start one month prior to admission
  Continue Itraconazole even if started on Ambisome
  Stop Itraconazole 2 weeks post discharge in all patients if ANC >1x10⁹ except those with acute GvHD or on steroids.
  N.B. Cyclosporin levels will decrease (over 1 - 2 weeks) from stopping Itraconazole
- Ciprofloxacin po 7.5 mg/kg
  NB Do not put down N/G tubes
• **3 weekly Gammaglobulin** (0.5g/kg) IV start on admission.
  Continue IVIgG 3 weekly until recovery of IgM and IgA and CD4 >300, but continue in those patients still on steroids or with chronic GvHD.

• **Ursodeoxycholic acid** 10mg/Kg twice a day orally if high risk for VOD

• **Paramomycin.** 10 mg/kg od + **Azithromycin** 10 mg/kg od if previous cryptosporidium

• **Aciclovir:** To start D-1 on patient receiving Fludarabine and on D-5 if receiving ordinary conditioning
  - If CMV neg/neg give 250 mg/m² tds iv
  - If patient or donor CMV pos then 500 mg/m² tds iv
  - Continue until Cyclosporin is stopped and CD4 >300.
  - If previous problems with CMV infection or excreting CMV prior to BMT, consider Ganciclovir/Foscarnet

• **Consider Liposomal Amphotericin** (Ambisome) 1 mg/kg/day from D -1 if previous fungal infection or prolonged neutropenia or unable to tolerate/absorb Itraconazole.

• **G-CSF** 5 mcg/kg/day iv starting D+8 and continue until ANC > 0.5 x 10⁹/l on two consecutive days and wean.
  - For all patients keep ANC > 0.5 x 10⁹/l with intermittent G-CSF as required.

• **Seprin** (7.5 mg/kg po bd) till D-1 regardless of neutrophil count.
  - Restart post transplant when ANC >0.5, according to doses below
    - <0.5m² 15mg/kg bd po Monday/Tuesday
    - 0.5-0.75m² 240mg bd po Monday/Tuesday
    - 0.76-1.0m² 360mg bd po Monday/Tuesday
    - >1.0m² 480mg bd po Monday/Tuesday
  - Continue to 3 months in autografts; in allografts until Cyclosporin is stopped and CD4 >300.
  - Pentamidine nebuliser 4 weekly (300 mg as >5 years -) or IV 2 weekly if unable to tolerate Seprin. If < 5 yrs and unable to tolerate nebulised give iv Pentamidine.
  - Folinic acid 15mg po weekly (Fridays) post BMT when on Septrin

• **Penicillin** po 125mg (250 mg - (>5 yrs) bd to start in all patients prior to discharge and to continue for minimum of 2 years and until proven good antibody response to Pneumococcal antigen. Continue life long if previous splenectomy.

• **Vitamin K** IV 300mcg/kg up to max dose 5mg weekly from D0, stop on discharge when Septrin starts.

• **Vitamin E** orally 100mg (>1year) daily when TPN starts. Stop when off TPN.

• **Fluoride** 2.2mg Fluotabs (>4 years) daily.

**REMEMBER:**
• **Converting IV to oral Cyclosporin:** oral dose = approx x 2-3 IV dose

If you should face adverse events, please inform as soon as possible the coordinator of this study:

**Paul Veys – Email : VEYSP@gosh.nhs.uk**
**CONDITIONING**  
Camp/Fludarabine/Melphalan

**BMT DONOR**  
MUD (10/10) / UD (9/10)

**Stem cell Source**  
BM or PBPCs [PBPCs preferred for UD 9/10]

**GVHD PROPHYLAXIS**  
CYCLOSPORIN (+MMF if using PBPCs)

**DIAGNOSIS**  
Non-SCID Immunodeficiency

**D-14**  
Admit to Fox BMT ward

**D-9**  
Start Allopurinol 4 mg/kg po tds for 6 days  
Continue Itraconazole  
IVIG  
Ciprofloxacin  
Seprtin

**D-8**  
Campath 1H, 0.2 mg/kg with pre-med

**D-7**  
Fludarabine 30 mg/m² (iv infusion over 30 minutes)  
Campath 1H, 0.2 mg/kg with pre-med

**D-6**  
Fludarabine 30 mg/m²  
Campath 1H, 0.2 mg/kg with pre-med

**D-5**  
Fludarabine 30 mg/m²  
Campath 1H, 0.2 mg/kg with pre-med

**D-4**  
Fludarabine 30 mg/m²  
Campath 1H, 0.2 mg/kg with pre-med

**D-3**  
Fludarabine 30 mg/m²

**D-2**  
Pre-Melphalan hydration: 4% dextrose/0.18% saline + 20 mmol/l of KCl at 200 ml/m²/hr for 3 hrs  
Melphalan 140 mg/m² (iv bolus push)  
Post-Melphalan hydration: 0.45% saline/2.5% dextrose + 40 mmol/m²/24 hrs of KCl at 3 l/m² for 24 hrs

**D-1**  
Cyclosporin 1.5 mg/kg iv twice daily  
Stop Seprtin  
Start Aciclovir

**D 0**  
Infusion of BM  
Minimum CD34 → 3 x 10⁶/kg  
If use PBPCs add MMF 15mg/kg tds orally from D0 to D27 – continue or tail depending on presence or absence of GVHD  
Start Vit. K

**D+8**  
Start G-CSF
I/ Guidelines for Autologous stem cell transplantation for Autoimmune Disease Juvenile Idiopathic Arthritis (JIA)

Revision and studied by Nico Wulffraat

I1. Indications:
Drug resistant form of systemic onset polyarticular JIA or Polyarticular JIA. Drug resistance must include corticosteroid dependancy to control symptoms such as the fever and arthritis. In addition patient must be resistant to Methotrexate or the anti TNF biological agents such as etanercept and infliximab, or suffer from serious side effects of these agents.

I2. Pre transplant work up
Unprimed bone marrow, harvested at least one month prior to ASCT, or PBSC after mobilisation (using cyclophosphamide at 1.5-3g/m2 and granulocyte colony-stimulating factor (G-CSF) at 10µg/kg/d). Graft processing using CD34 selection devices.
Assess clinical JIA activity using PRINTO core set criteria.
Radiographs of all affected joints.
Dexascan.
Screen for haemophagocytosis/MAS in marrow. Screen for infections, mostly viral and tuberculosis (especially after anti TNF treatment).
Lab : ESR, fibrinogen, tryglycerids, ferritin
Immunological lab : lymfocyte subsets and function, Store cells (CD4 ; CD8 separately if possible) and plasma/serum. Ig’s

I3. When to perform the transplant
Previous studies suggested that reactive hemophagocytosis might be prevented by pre-treatment of corticosteroids in cases with persisting fever.

I4. Conditioning
After 3 events of severe hemophagocytosis, possibly related to Fludarabin in SCT for systemic onset JIA, the previous conditioning regimen is in use again. Several options are possible.
Standard protocol :
• ATG (Rabbit) 4x5mg/kg, day –9 to -6
• Cyclophosphamide 4x50mg/kg, day –5 to -2
• Total Body Irradiation (4Gy) day –1 or Busulphan 4 x 2mg/kg at day –9 to –6

I5. Supportive therapy
Prophylaxis with antibiotics and antimycotics. PCR guided anti viral treatment. Corticosteroids must be tapered slowly. Anti TNF treatment must be stopped before SCT. MTX can be stopped shortly before the conditioning.

If you should face adverse events, please inform as soon as possible the coordinator of this study

Nico M Wulffraat (Wilhelmina Children’s Hospital – The Netherlands) Tel : 31.30.2504003 – Fax : 31.30.2505350 – Email : n.wulffraat@whz.azu.nl