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Sequential HSCT and Renal Transplantation – A case study

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Health

Girl receives UK's first rejection-free kidney from mum

3 days ago

Aditi is taking no anti-rejection medication - and her new kidney is working

By Michelle Roberts
Digital health editor

Eight-year-old Aditi Shankar has become the first child in the UK

Drug-free kidney transplant

Aditi Shankar, eight, had *her immune system 'reprogrammed' so that donor organ was accepted*

By **Laura Donnelly** HEALTH EDITOR

AN eight-year-old girl has become the first person in the UK to receive a kidney transplant without having to take lifelong drugs.

Aditi Shankar's immune system was "reprogrammed" after a stem cell transplant, allowing her body to accept a donor kidney as its own, medics said.

Because the bone marrow transplant and kidney came from the same donor, Aditi's mother, the new kidney is working without the need for drugs that stop the body from rejecting a donated organ.

Medics said they were "excited" by the UK first, which has left the little girl fighting fit with an excellent immune system as well as a new kidney.

They added the high-risk operation might benefit other patients with par-

Just last year, the child spent a significant proportion of time in and out of hospital to receive dialysis – a procedure that removes waste products and excess fluid from the blood when the kidneys have stopped working properly.

To receive dialysis, Aditi travelled from her family home in Greenford, north-west London, into the city centre for treatment at least three times a week.

Aditi was first referred to Great Ormond Street Hospital (GOSH) in London at the age of five, where doctors discovered she had a rare genetic condition called Schimke immuno-osseous dysplasia, which affects the immune system and kidneys.

For every three million children in the UK, doctors are likely to only find one case.

In March 2021, her kidney function dropped drastically, but a kidney transplant was not possible while her immune system was so weak.

The renal, immunology and stem cell transplant teams at GOSH worked with international colleagues to come up

was in the
a bone mar-
lso received
arch 2023,
the kidney
new blood

cells," Aditi said. "I got the kidney transplant when I went to special sleep and closed my eyes.

"Now I have got the line out, I can go swimming."

Aditi said her school is scienc interest in biol much about th her time in hos

ave

Britain is tipped as

itv NEWS More

Girl, 8, gets UK-first kidney transplant without need for life-long drugs

GREAT ORMOND STREET | KIDNEY TRANSPLANT | NHS | Friday 22 September 2023 at 4:07pm

Aditi Shanker has received ground-breaking care for a rare genetic condition, Amy Lewis reports

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Brief Report | 1 June 1991

Immunologic Tolerance to Renal Allografts after Bone Marrow Transplants from the Same Donors

Authors: Mohamed H. Sayegh, MD, Neil A. Fine, MD, John L. Smith, MD, Helmut G. Rennke, MD, Edgar L. Milford, MD, and Nicholas L. Tilney, MD | AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

Publication: Annals of Internal Medicine • Volume 114, Number 11 • https://doi.org/10.7326/0003-4819-114-11-954

- Two patients – received HSCT from HLA identical siblings for leukaemia.
- Both then developed renal failure a few years post transplant.
- Both received kidneys from the same sibling donors.
- Both maintained only on low dose steroids with stable renal function.

Why?

- Achieving tolerance is the holy grail!
- This could reduce/remove the need for immunosuppression.
- This should –
  - Reduce the morbidity and mortality associated with IS
  - Reduce IS associated graft damage
  - Reduce infection and cancer rates post transplant
  - Remove the need for IS compliance
- Michael Eder et.al. multicentre analysis –
  - Improved graft function and graft survival in ‘tolerant group’

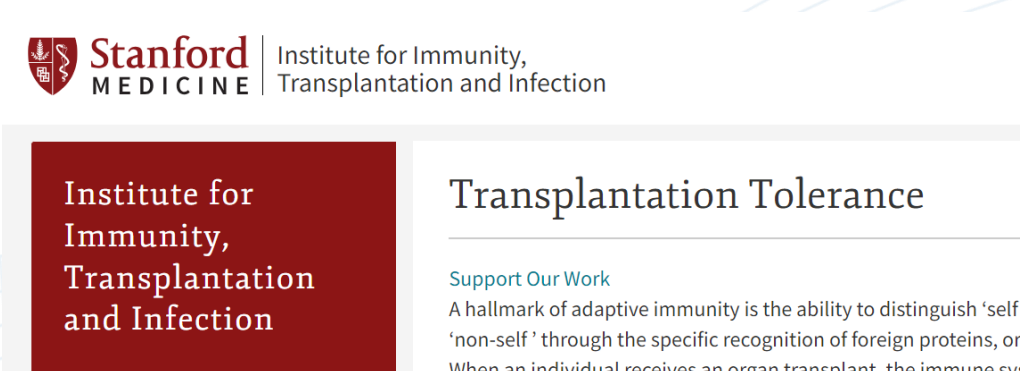
Why not?

- Controversial.
- HSCT and conditioning come with serious potential risks
- GvHD, severe fungal, bacterial and viral infection – commonly reported in groups trying this.
- In majority of cases patients would do acceptably well with conventional renal transplant and immunosuppression therapy.

- Michael Eder et.al. multicentre analysis –
  - Higher rate of death in ‘tolerant group’.

Growing momentum and different approaches:

- Multiple groups now looking at options – small patient numbers.
- HLA identical siblings to Haploidentical donors.
- Full chimerism or mixed chimerism (transient or stable).
- HSCT then kidney.
- Kidney then HSCT (potential to extend to deceased donors).
- Variety of conditioning regimens.
- Some ‘just’ trying to achieve tolerance.
- Others treating complex diseases that require/benefit from both types of transplant.

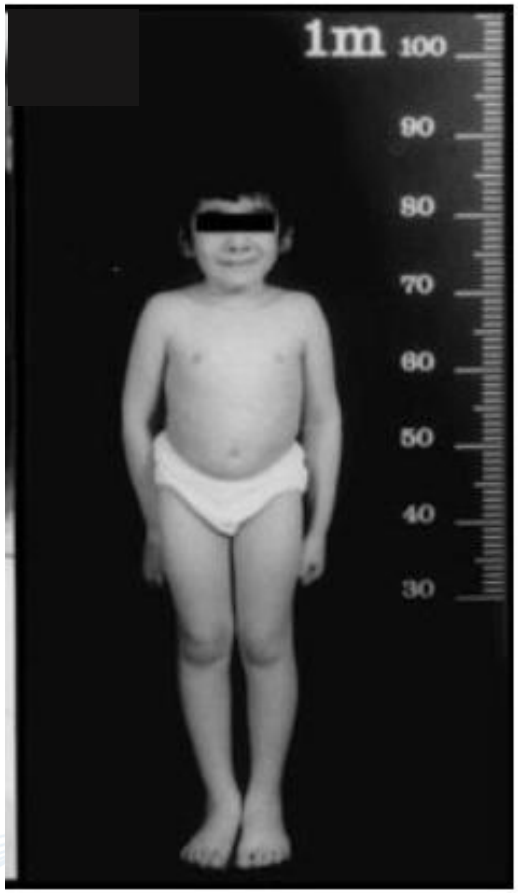


Schimke Immuno-osseous dysplasia (SIOD):

- Rare autosomal recessive multisystem disease.
- Caused by bi-allelic mutations in the gene SMARCAL-1
- Member of the SW12/SNF2 family of ATP-dependent chromatin remodelling proteins.
- Thought to regulate transcription of certain genes by altering the chromatin structure around those genes.
- Implicated in replication-coupled DNA repair and telomere maintenance.

Schimke Immuno-osseous dysplasia (SIOD):

- Characterised by –
  - Steroid-resistant nephrotic syndrome
  - Short stature – short trunk, neck and limbs, normal sized hands and feet
  - Variable T cell immunodeficiency
- Suffer severe infection, bone marrow failure, renal failure and pulmonary disease.
- Increased risk of haematological malignancy.
- Incidence is 1 in 1 – 2 million live births
- SIOD is either severe with early-onset symptoms starting as an infant, or mild with late-onset symptoms starting in the teen years.



Schimke Immuno-osseous dysplasia (SIOD):

- Average life expectancy is 9.2 years
- This is increased if the renal disease is treated by transplant
- Traditionally treatment has been to manage symptoms –
  - Dialysis and eventual kidney transplantation for renal disease
  - Stem cell transplant is sometimes used to treat immunodeficiency and blood abnormalities
- Alone neither treatment has been very effective.

Stem cell transplant for SIOD:

- Previous attempts to treat SIOD with a stem cell transplant were poor.
- SIOD patients are more at risk following myeloablative conditioning due to SMARCAL-1 deficiency leading to increased sensitivity to the drugs.
- For example – Baradaran-Heravi et.al.
  - 5 children with SIOD received HSCT after myeloablative conditioning.
  - 4 died from HSCT-related causes – infection and GVHD
  - 1 was successful.
- A new approach was needed.

Renal Transplant for SIOD:

- Renal transplantation alone has equally poor outcomes.
- Due to SMARCAL-1 mutation IS post transplant is associated with high post-transplant mortality due to severe infections and post-transplant lymphoproliferative disease.
- For example – Woo et.al. reported a series in 2020 of three children receiving a kidney alone transplant –
  - 1 child died from infection 4 months post transplant.
  - The two other children suffered multiple infections requiring prolonged hospitalisation
  - Both lost their grafts 3 & 5 years post transplant due to rejection
- A new approach is needed.
- The aim would be to transplant without the need for immunosuppression.

Kidney after HSCT – the theory:

- This can be achieved by HSCT followed by kidney transplant from the same donor.
- The HSCT will replace the child's immune system, the subsequent transplant can then be accepted without IS.

Kidney after HSCT – the reality:

- Most donors will be haploidentical parents.
- Requires either full replacement of immune system or establishment of stable mixed chimerism.
- In non-HLA matched donors and recipients stable mixed chimerism has only allowed a reduction in IS, not it's discontinuation.
- Previous attempts 'Complicated' by fatal GVHD (quite the complication!).

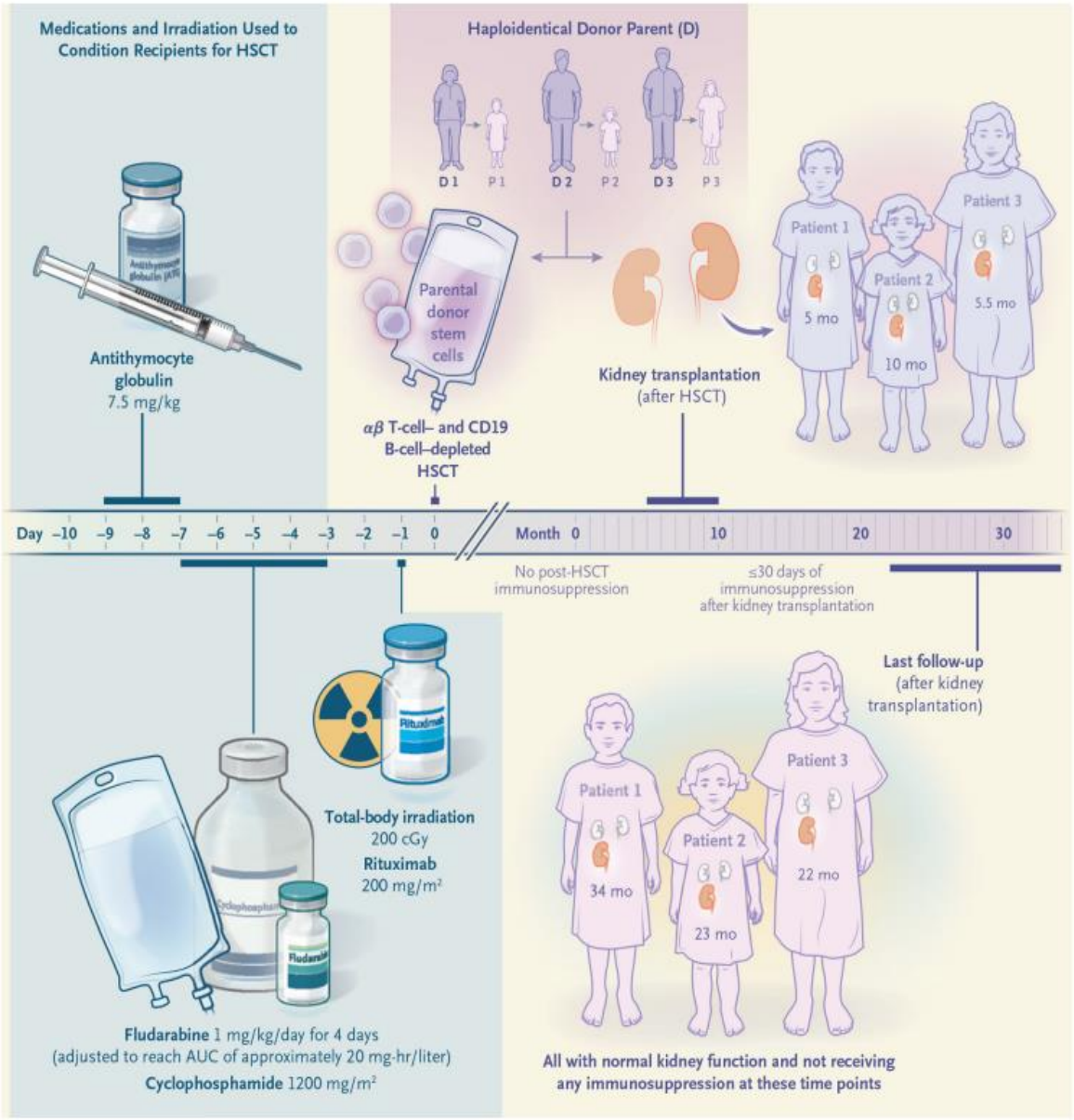
αβ T-cell depleted haplo transplants

- Protocol developed by Alice Bertaina et.al. to improve outcomes in patient with only haploidentical donors available.
- αβ T-cells thought to be responsible for GVHD.
- Selective depletion of αβ T-cells and CD19 B cells for haploidentical HSCT has been used successfully in patients transplanted due to non-malignant disease.
- 90% survival rate.
- Low rates of acute and chronic GVHD and transplant related deaths.
- In a trial of 70 adults with non-malignant disorders there were no deaths following reduced-intensity conditioning and transplant.
- This included patients with radiosensitive conditions – similar to SIOD.

αβ T-cell depleted haplo transplants

- The same group used this approach to HSCT to transplant 23 children with non-malignant disorders.
- Differing conditioning depending on original disease.
- All received 2 x ATG on days -5 and -3 to prevent rejection and GVHD.
- All received rituximab on day -1.
- 21 of 23 engrafted, but overall graft failure of 16.2% (4 children).
- All successfully re-grafted with same donor (2) or other parent (2).
- 3 patients had grade 1 or 2 GVHD
- At 18 months follow up 21 of 23 were alive and disease free.

αβ T-cell depleted haplo then Kidney transplants:



- The same group published the first three SIOD recipients of this new approach in 2022.
- Received αβ T-cell depleted and CD19 B cell depleted haploidentical HSCT from a parent.
- When full donor myeloid and lymphoid chimerism was confirmed the patient received a kidney from the same parent.
- No IS after day 30.
- At 22 – 30 months post renal Tx all had normal function and no sign of rejection.
- All had corrected their primary immunodeficiency.

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GOSH case - AS

- Presented to GOSH in 2020 age 5 with classic symptoms of SIOD –
  - Steroid resistant nephrotic syndrome
  - Dysmorphic features
  - Short stature
- Homozygous SMARCAL-1 mutation confirmed.
- Reached ESRD and started HD in May 2021.
- Both parents (and 13 year old brother) assessed for transplant options.

Initial typing and work up:

- Family sent for HLA typing and antibody screening in May 2021.
- As expected both parents were 111 mismatches.
- HLA antibody negative.
- All were blood group O.

	A		B		C		DRB		DR3/4/5		DQB	
Patient	2	3	40:06	56	1	12	1	13	52		5	6
Mother	3	33	40:06	44	7	12	7	13	52	53	2	6
Father	2	68	56	58	1	10	1	10			5	

Stem cell transplant:

- Decision made to proceed with the mother as a donor.
- Combined transplant approved by the hospital ethics board.
- Patient received αβ T-cell and CD19 B cells depleted haploidentical stem cell transplant from her mother in September 2022.
- Conditioning consisted of – ATG, Fludarabine, Cyclophosphamide, TBI (200cGY) and Rituximab.
- HD switched to continuous haemofiltration for 24 days to support fluid control during conditioning/chemotherapy.
- Developed mucositis and mild skin GVHD treated with IV pred.
- Resolved and discharged at 40 days.
- Remaining post stem cell period was uneventful and full chimerism achieved.
- Reverted to HD to await kidney transplant.

Renal Transplant:

- HLA typing was repeated on the patient in February 2023.
- Confirmed HLA type was now consistent with her mother.
- A final flow crossmatch was performed in February 2023, 2 weeks prior to the scheduled transplant – this was negative.
- A renal transplant from the mother was performed on 7/3/23.
- No induction therapy
- IV methylpred given on day of transplant
- Switched to oral, at a tapering dose from days 1 to 28
- Low dose oral tacrolimus given days 1 – 35.
- All IS ceased on day 35.
- EBV reactivation noted post transplant, treated with single IV dose of Rituximab on day 79.
- Remaining post transplant course uneventful.

Now:

- Currently 23 months post stem cell and 18 months post renal transplant – 17 months without IS.
- Serum Cr is 25umol/l.
- No recent infections and doing very well.

Case 2?

- 2nd case in work up.
- Significantly more complicated.
- Adoptive parents – poor match and ABOi.
- Birth mother ruled out as donor option.
- Currently aiming for haplo HSCT from donor registry.
- Followed by renal transplant from adoptive father.
- Aiming for some matching between adoptive father and donor….yikes!
- Significantly poorer health – history of B cell ALL, encephalitis and other infections.
- Aiming for HSCT in next few months, then will assess options for renal transplant.

The next steps:

- There are more to come.
- At least one other patient is undergoing the process at GOS.
- Two children are starting at ECH.
- Main issue is getting the communication from the teams around types and transplants.
- Could give future to these children who otherwise wouldn't survive.
- Now investigating this as an option to treat other causes of renal failure – FSGS, SLE caused renal failure and Cystinosis.

May 05, 2023 | 3 min read SAVE

Researchers successfully transplant stem cells to protect donor kidney

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Adding stem cells to a kidney transplant could get patients off anti-rejection drugs, trial finds

Finding a way to keep a patient off of immunosuppressant drugs is considered the "holy grail" of organ transplantation, experts say.

Young Man Becomes First in World to Be Cured of FSGS With New Treatment

October 4, 2022 | Lynn Nichols

PATIENT STORIES.

Thank you!

- Professor Steven Marks
- Maria Scanes