HCA Healthcare UK

NHS

Update in desensitisation strategies

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4th GCC Organ Transplantation & Nephrology Conference

Overview

- Sensitisation and access to transplantation
- Options for the sensitised patient
- Novel approaches to desensitisation - Imlifidase

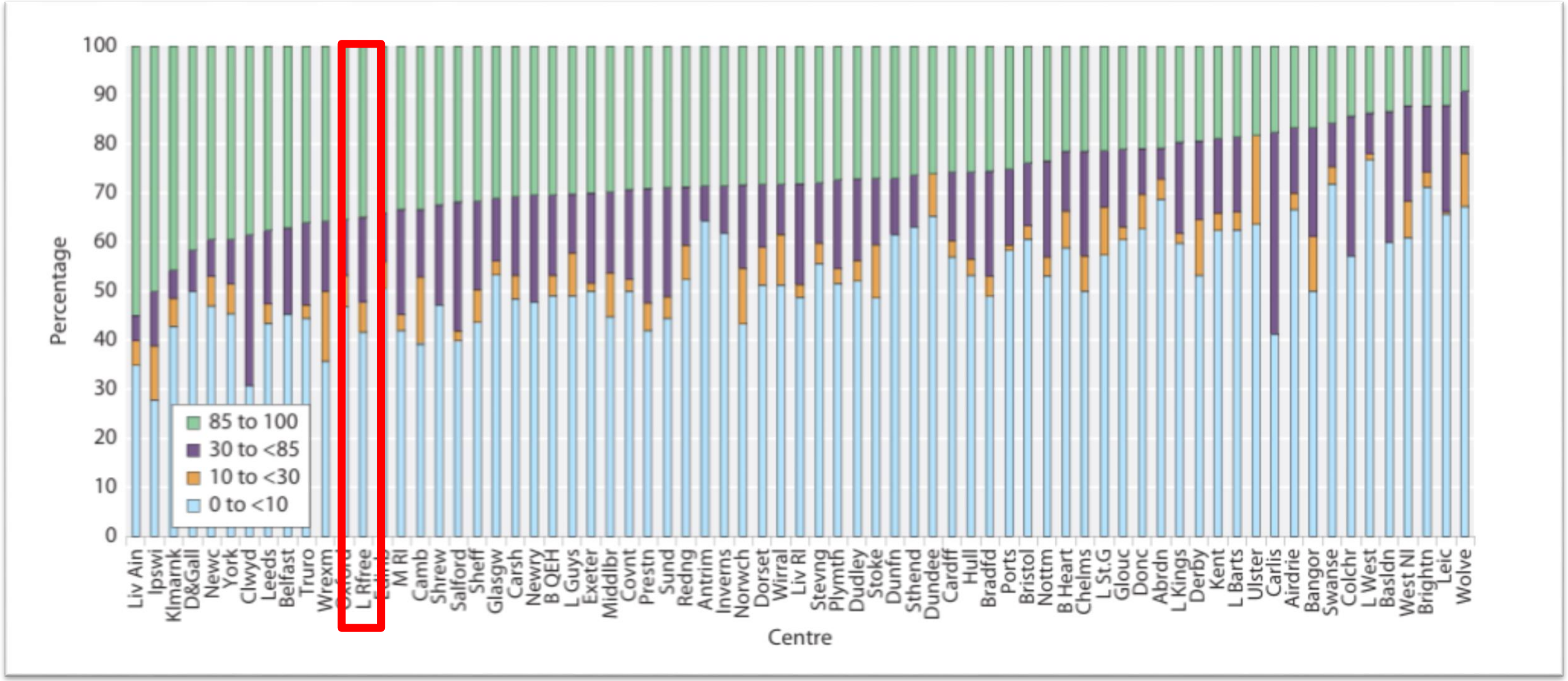
Scale of the problem

- 30 - 40% of patients awaiting a kidney transplant in the UK are highly sensitised

- Around 10% have cRF 100%

- Median time to transplantation > 6 years (vs median approx. 18 months)

Proportion of patients highly sensitised



UK Renal Registry data

Options for the highly sensitised patient

Waiting

- National deceased donor list
- Kidney sharing schemes
- Priority allocation to highly sensitized recipients

De-listing

- Ignoring selected low-level HLA antibodies in the allocation process

Desensitisation

- Reduce higher levels of HLA antibodies down to permissive levels that can then be ignored.

Risks of desensitisation

- Higher rates of early and late aggressive rejection

- Shortened graft half-life

However:

- Survival at least equivalent to (UK) or better (USA) vs remaining on the waiting list

Conventional strategies for desensitisation

Apheresis

- Plasma exchange
- Immunoadsorption

Intravenous immunoglobulin(IVIG)

Anti-CD20 antibodies

- Rituximab

Novel strategies for desensitisation

Proteasome inhibitors

-Bortezomib (Velcade)

-Induces apoptosis in plasma cells

IL-6 inhibitors

- Tocilizumab

- Target follicular Th and plasma cells

Complement inhibition

- Eculizumab

Anti-CD38 antibodies

- Daratumumab, isatuximab, carfilzomib

- Targets plasma cells

Co-stimulation blockade

- Belatacept

-May prevent DSA rebound

Anti-BAFF Agents

- Belimumab

Novel strategies for desensitisation - Imlifidase

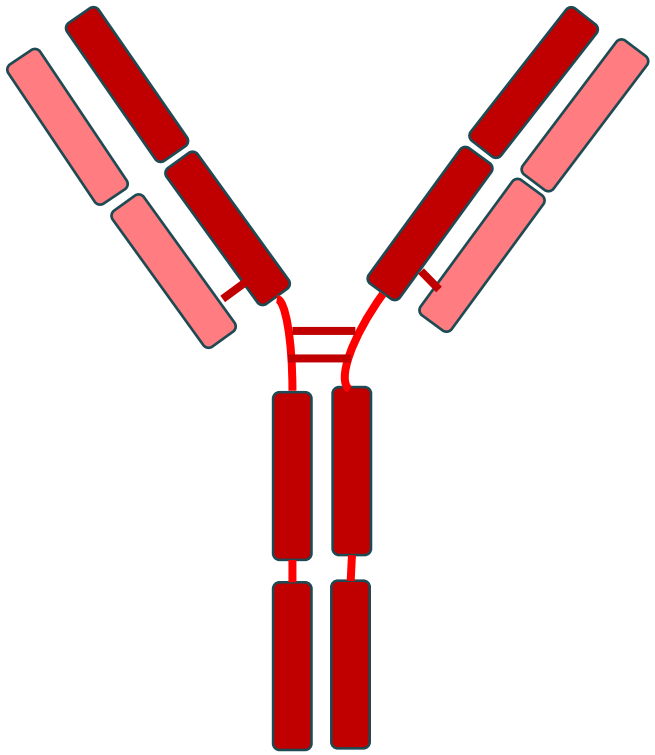
IgG endopeptidase

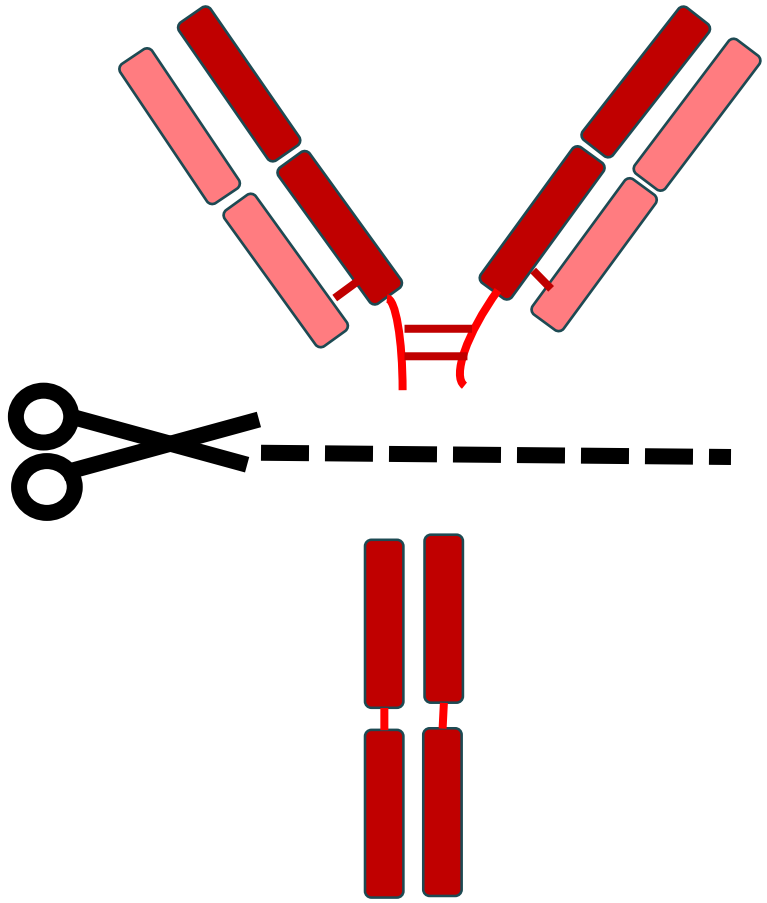
-Cysteine protease identified in group A streptococci

- Inactivates opsonizing IgG antibodies bound to the bacterial surface (IgG-degrading enzyme of Streptococcus pyogenes - IdeS)

- Specifically cleaves IgG molecules

IgG





FAb

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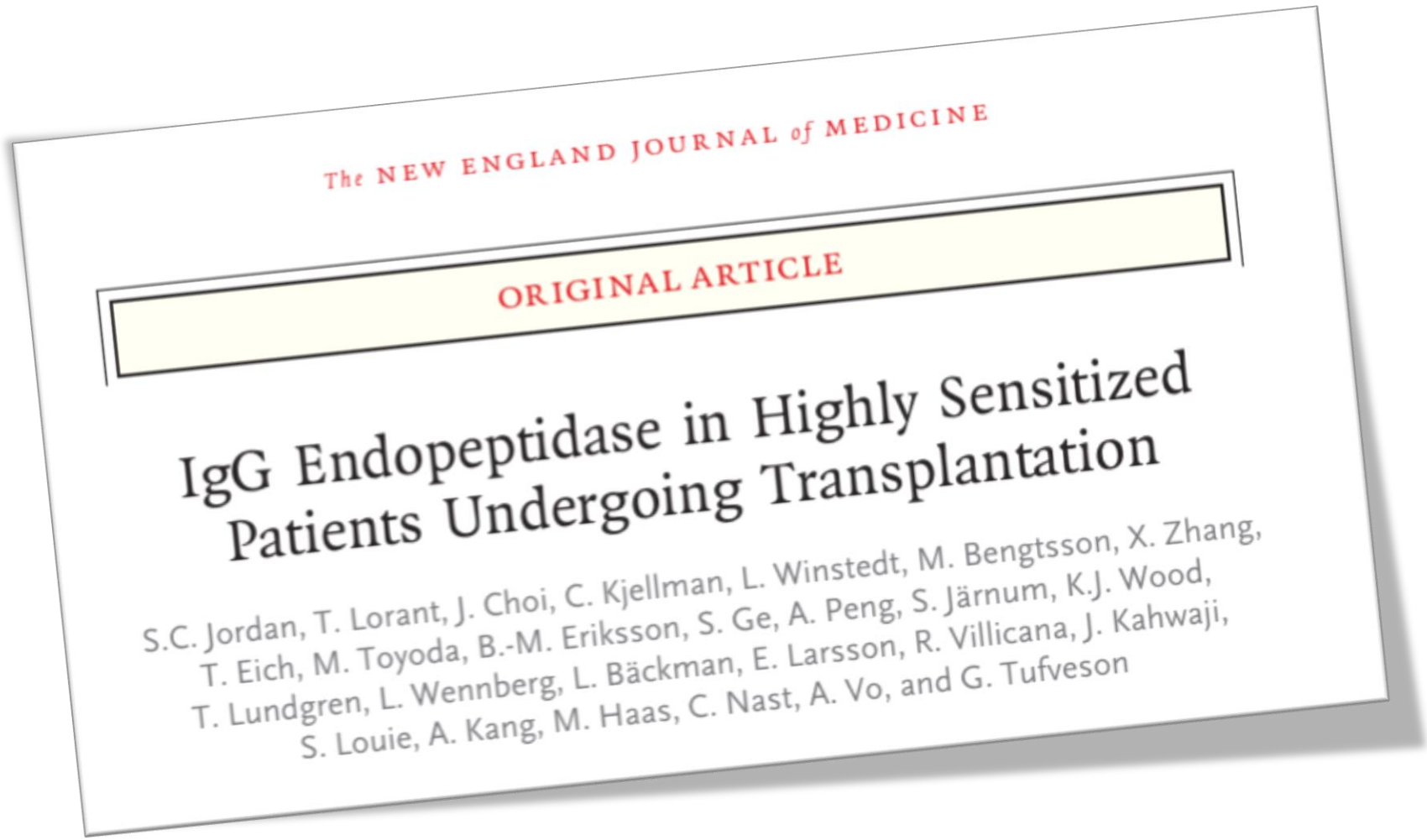


N Engl J Med 2017;377:442-53

Patient characteristics

25 highly HLA-sensitized patients

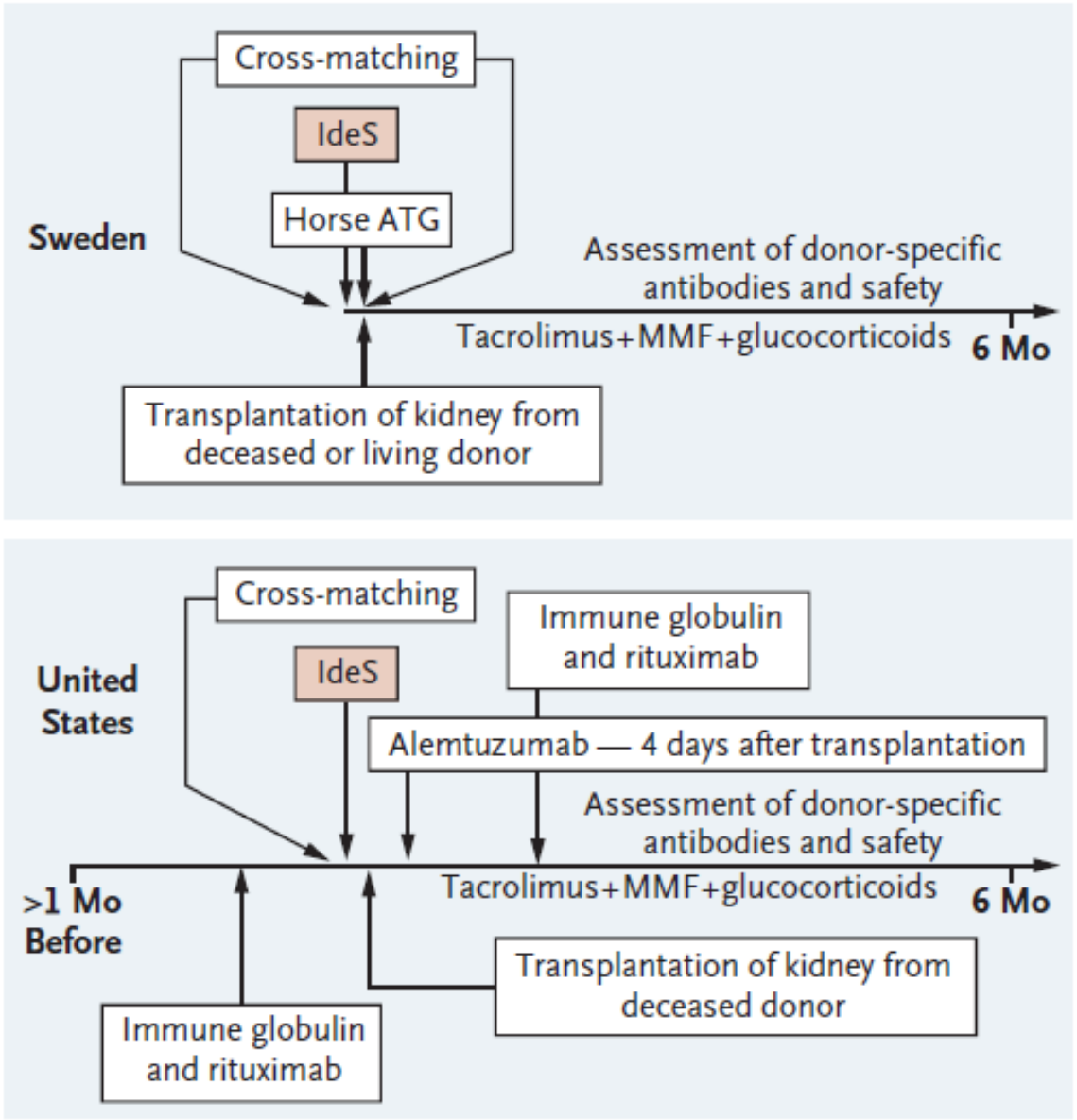
- Sweden N = 11
- USA N = 14

Number of DSA = 2.3 +/- 1.8

Mean MFI – 5,660 (class I) and 8,199 (class II)

N Engl J Med 2017;377:442-53

B Immunosuppressive Regimens



N Engl J Med 2017;377:442-53

Outcomes

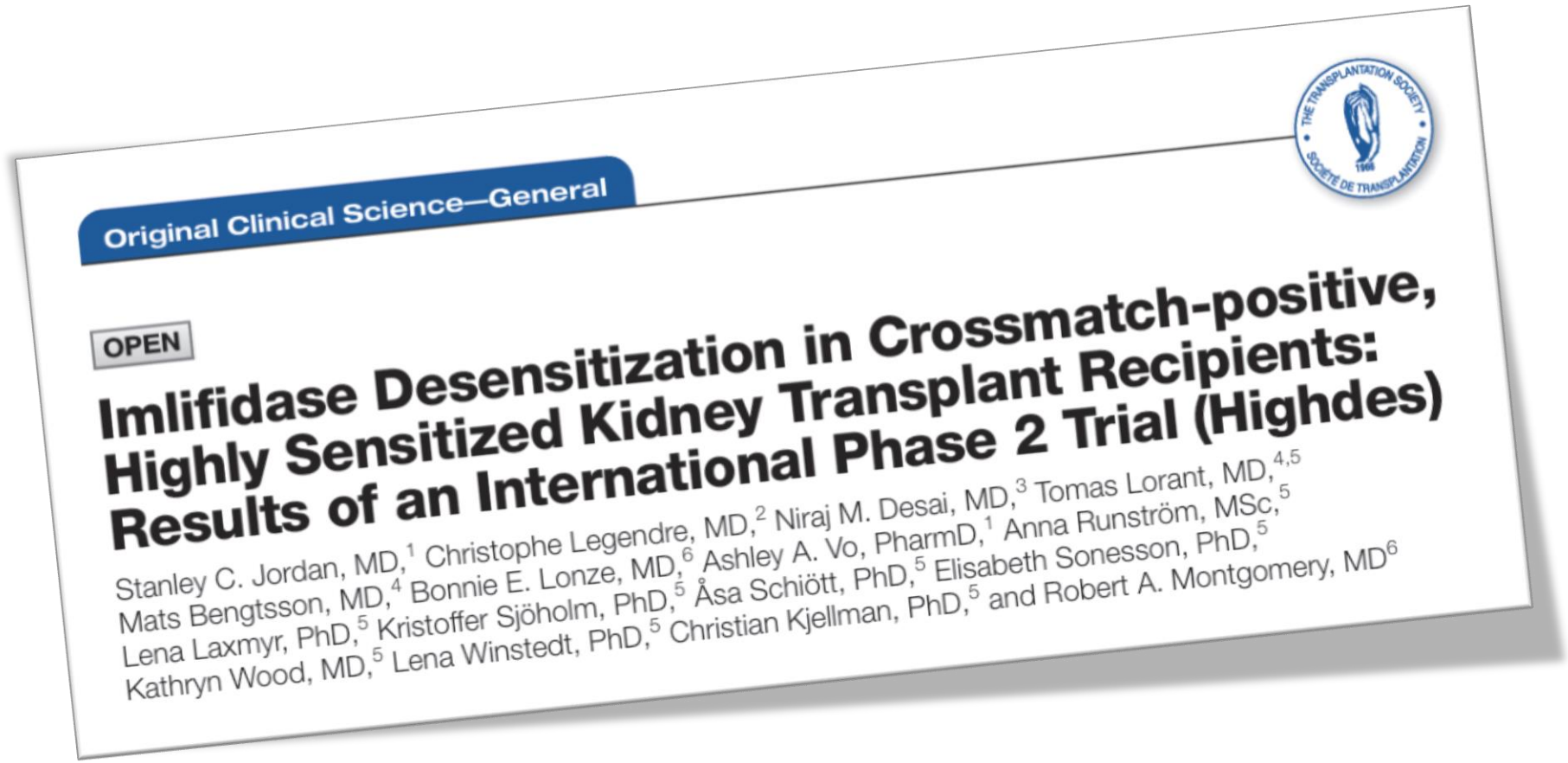
Antibody mediated rejection 10/25 patients (40%) in first 5 months

All had a response to treatment

One graft loss, mediated by non-HLA IgM and IgA antibodies

Mean eGFR at 1–6 months after transplant 58ml/min

N Engl J Med 2017;377:442-53



Transplantation 2021;105: 1808–1817

Trial design

- Open-label, single-arm, phase 2 trial
- Five centres (France, USA, Sweden)
- Patient median cRF 99.8%

Transplantation 2021;105: 1808–1817

Highdes trial

19 enrolled

1 excluded due to AE with imlifidase

18 transplanted

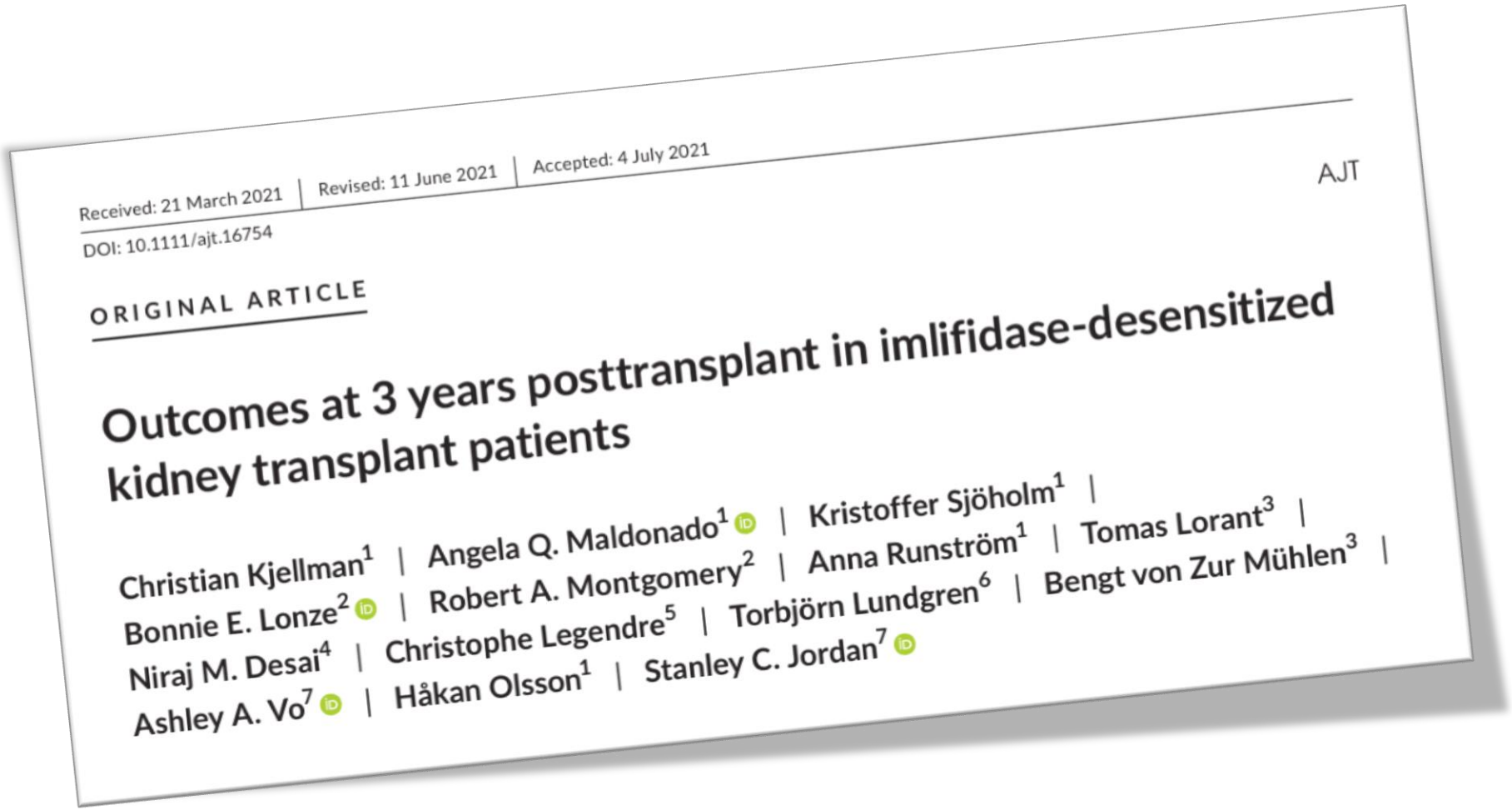
2 primary non-function

Transplantation 2021;105: 1808–1817

Highdes trial

- Patient survival 100%
- Graft survival of 89% at 6 months
- ABMR rate 39% (biopsy proven)
- Onset 2–19 days post-transplantation

Transplantation 2021;105: 1808–1817



Received: 21 March 2021 | Revised: 11 June 2021 | Accepted: 4 July 2021

DOI: 10.1111/ajt.16754

ORIGINAL ARTICLE

Outcomes at 3 years posttransplant in imlifidase-desensitized kidney transplant patients

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Am J Transplant. 2021;21:3907–3918

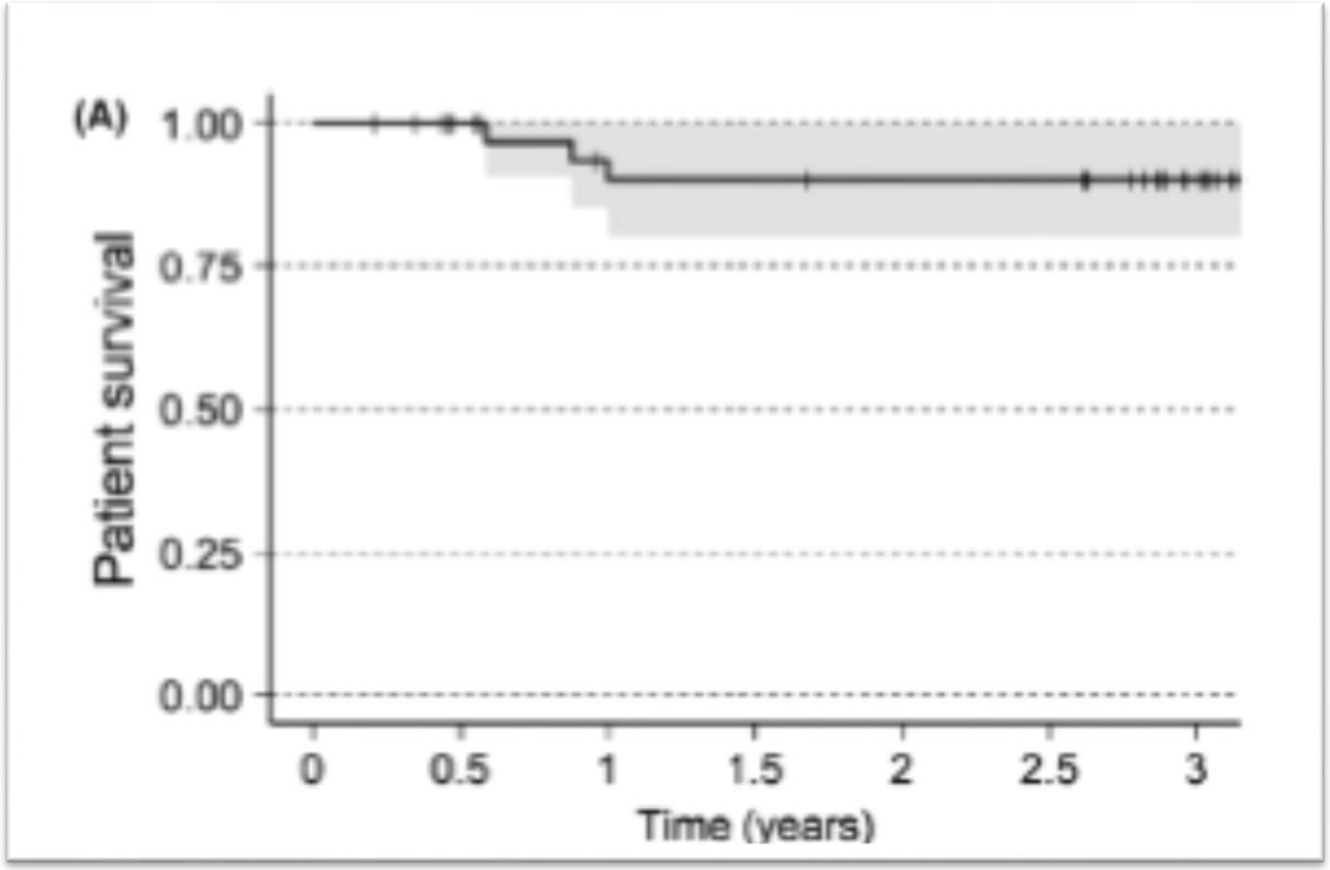
Transplant outcomes at 3 years

- Combined data from four single-arm, open-label, phase 2 studies

- N = 39 patients

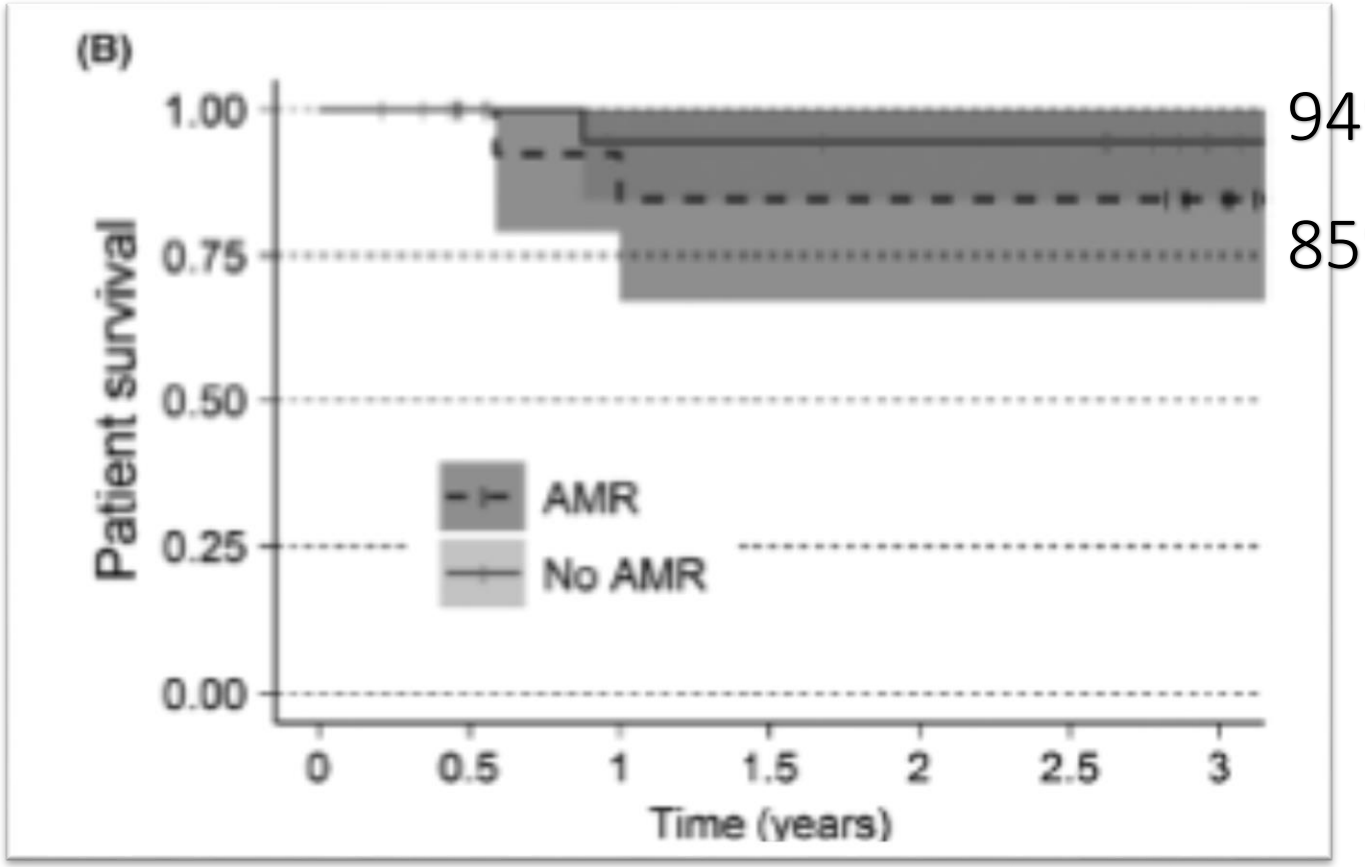
Am J Transplant. 2021;21:3907–3918

Patient survival

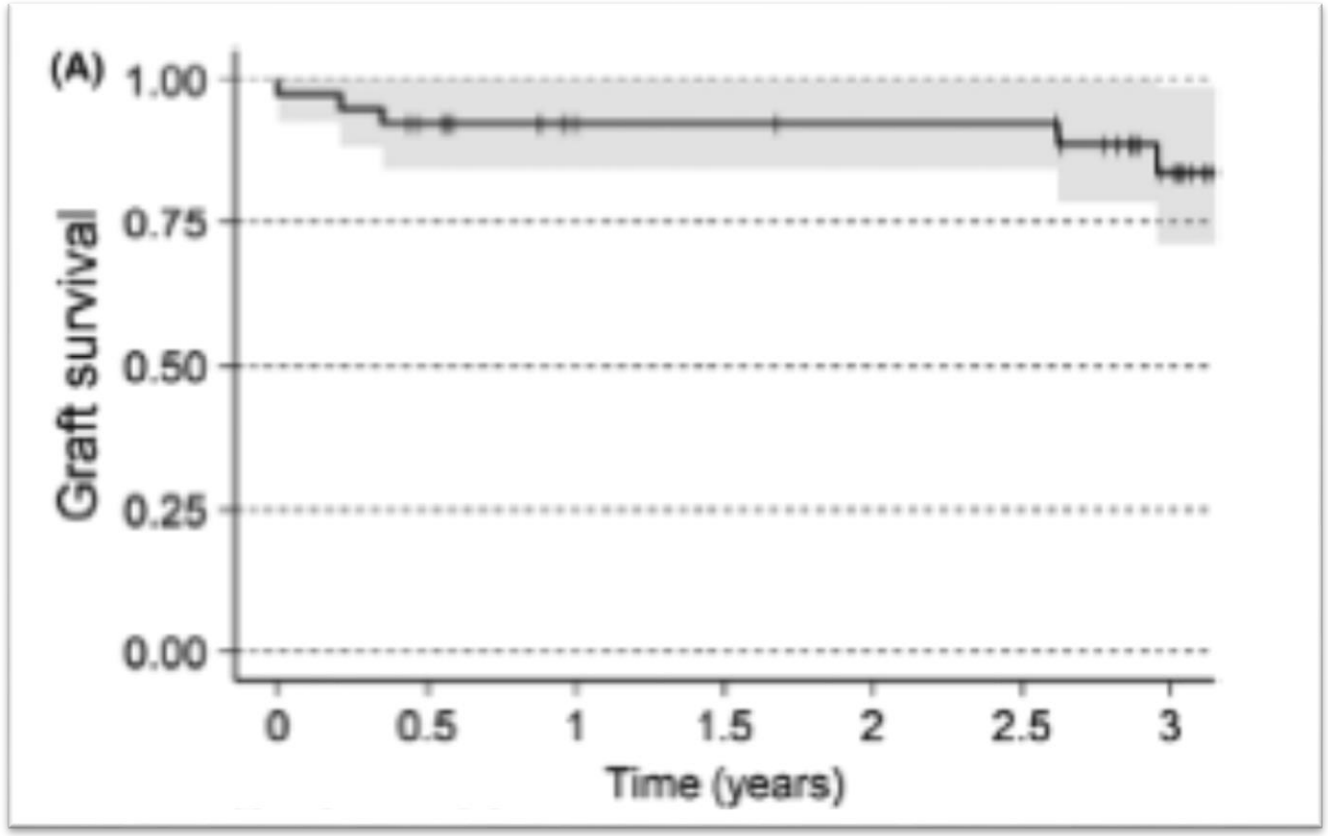


90%

ABMR associated with higher mortality, lower GFR



Death-censored graft survival



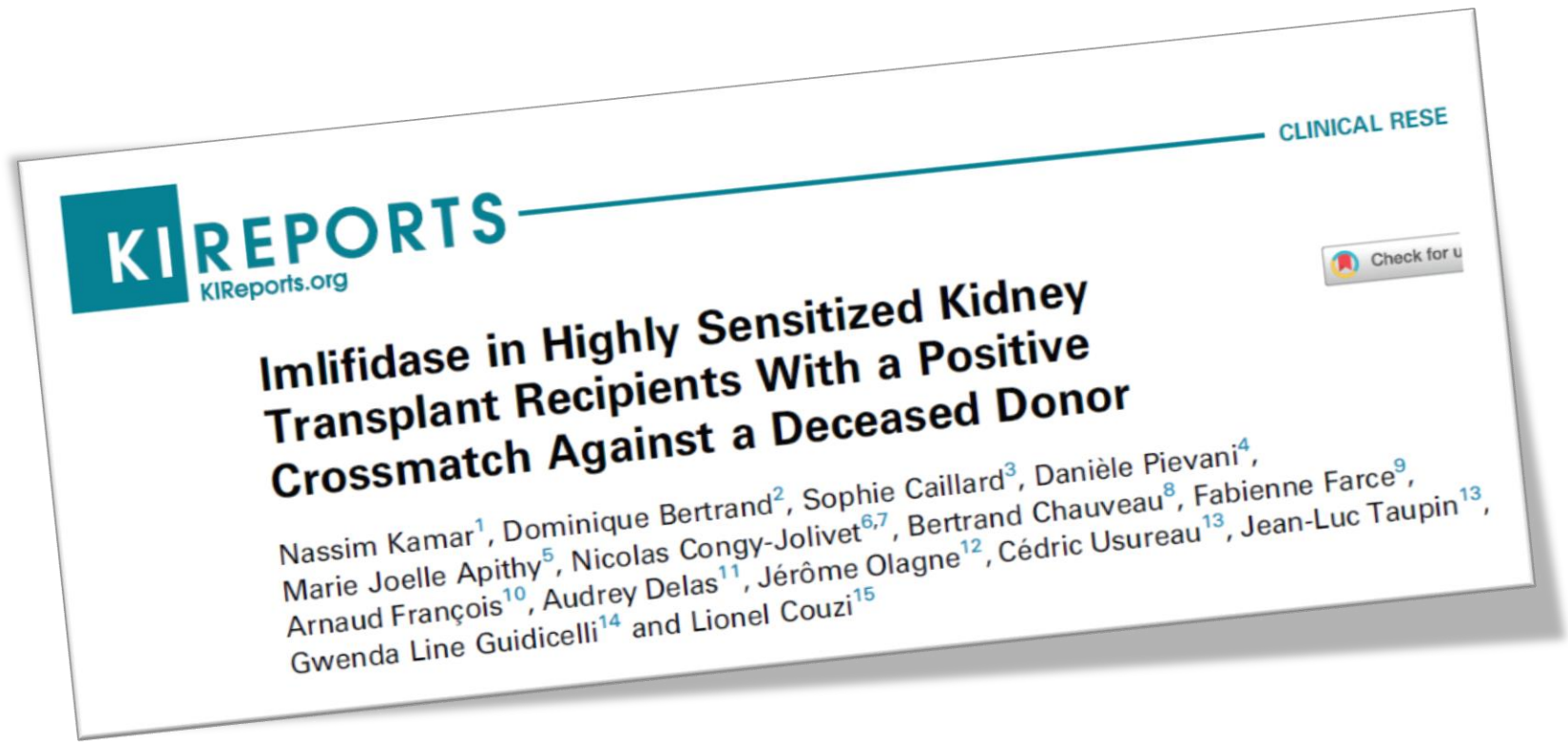
84%

Graft outcomes

- Mean eGFR 55 ml/min/1.73 m2 at 3 years

- Highly sensitized patients (cPRA ≥ 99.9%), had higher rates of AMR

Am J Transplant. 2021;21:3907–3918



Kidney Int Rep (2024) 9, 2927–2936

Patient characteristics

- N = 9 patients
- Calculated PRA 98%
- Waiting time 3 years
- Immunodominant DSAs with MFI > 6000 (and < 5000 at 1:10 dilution)

Outcomes

All achieved a negative CDC and flow crossmatch

Immunosuppression:

- IVIg + rituximab + ATG + tacrolimus + mycophenolate

Five patients had a DSA rebound within 14 days

Outcomes

- Clinical ABMR = 2 patients
- Subclinical ABMR = 2 patients
- eGFR 56ml/min at 7 +/- 2.8 months
- No graft loss or death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New treatment to enable kidney transplant in highly sensitised patients
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Imlifidase for desensitisation treatment before kidney transplant in people with chronic kidney disease
Technology appraisal guidance | TA809 | Published: 20 July 2022

British Transplantation Society guidelines

Patient selection

- Calculated reaction frequency (CRF) of at least 99%
- Matchability score of 10
- On the waiting list for a transplant for at least 2 years
- Positive crossmatch (actual or predicted) with the donor
- Unlikely to have a transplant under the available kidney allocation system (including prioritisation programmes for highly sensitised people)

Donor selection

Caution with:

- Older donor
- Donor AKI
- Long cold ischaemia times

Step 1 – try delisting first!

De-listing

- Historic positive specificities
- Previous repeat mismatched HLA antigens (organ transplant)

….if currently negative on single antigen bead assays

- Include any specificities that have tested negative in three consecutive samples within the last 6 months or longer.

- Minimum target cRF < 99% to attract donor offers

Delisting

After 6 months if:

- No donor offers
- No further specificities can be de-listed

-> Imlifidase-enabled transplant

Preparing for imlifidase-enabled transplantation

- Stable HLA antibody profile (or falling)

- Start with weaker antibodies

- Avoid delisting repeat mismatches with previous transplants if possible

- Prioritise the de-listing of specificities for which the MFI of the related antibody shows clear reduction upon dilution at 1:16 or lower.

- Aim to achieve n/10,000 if possible ≥100 (CRF <99%)

Stepwise escalation

If no donor offers:

-Extend de-listing to include higher level antibodies

Caution with:

-Multiple de-listed unacceptable antigens (3 or more)

-High cumulative MFI

Review de-listed unacceptable antigens every 3 months (minimum)

On the day

Flow +/- CDC crossmatch

- Test at a minimum of 4 hours and ideally at 6 hours after drug administration complete.

If the crossmatch remains positive at six-hours post imlifidase

- > Transplant does not proceed

N.B. Have a back-up recipient (preferably suitable for virtual crossmatch)

Induction immunosuppression

IV Methylprednisolone

Give 500mg IV on day 0 then 125mg IV daily up to and including day +4

Lymphocyte depleting therapy

– Alemtuzumab 30mg IV or SC on day 4

OR

– Equine Anti Thymocyte Globulin (ATG) (3mg/Kg daily on days 1-3)

OR

Rabbit ATG 1.5mg/kg daily on days 4-7

Maintenance immunosuppression

“Triple therapy”

Calcineurin inhibitor + anti-proliferative + steroids

E.g. tacrolimus + mycophenolate / mycophenolic acid + prednisolone

Managing ABMR

- Extracorporeal antibody removal with a minimum of five treatments

- IV immunoglobulin
- After each treatment or at the end of treatment course

- High dose steroids

- Optimise baseline immunosuppression

- Considered other agents eg anti-CD20 therapy

Take home messages

- Careful donor and recipient selection

- Start cautiously

- Beware multiple DSA (>/= 3), high MFI, repeat mismatches with prev Tx

- “One in, one out”?