

IgG- Endopetidase

Neues Therapiekonzept zur Desensibilisierung?

V. SCHWENGER

KLINIK FÜR NIEREN-, HOCHDRUCK- UND AUTOIMMUNERKRANKUNGEN

TRANSPLANTATIONSZENTRUM STUTTGART

SENSIBILISIERUNG DES NTX-PATIENTEN

Vorsensibilisierung durch

Schwangerschaft

Bluttransfusionen

Nierentransplantationen

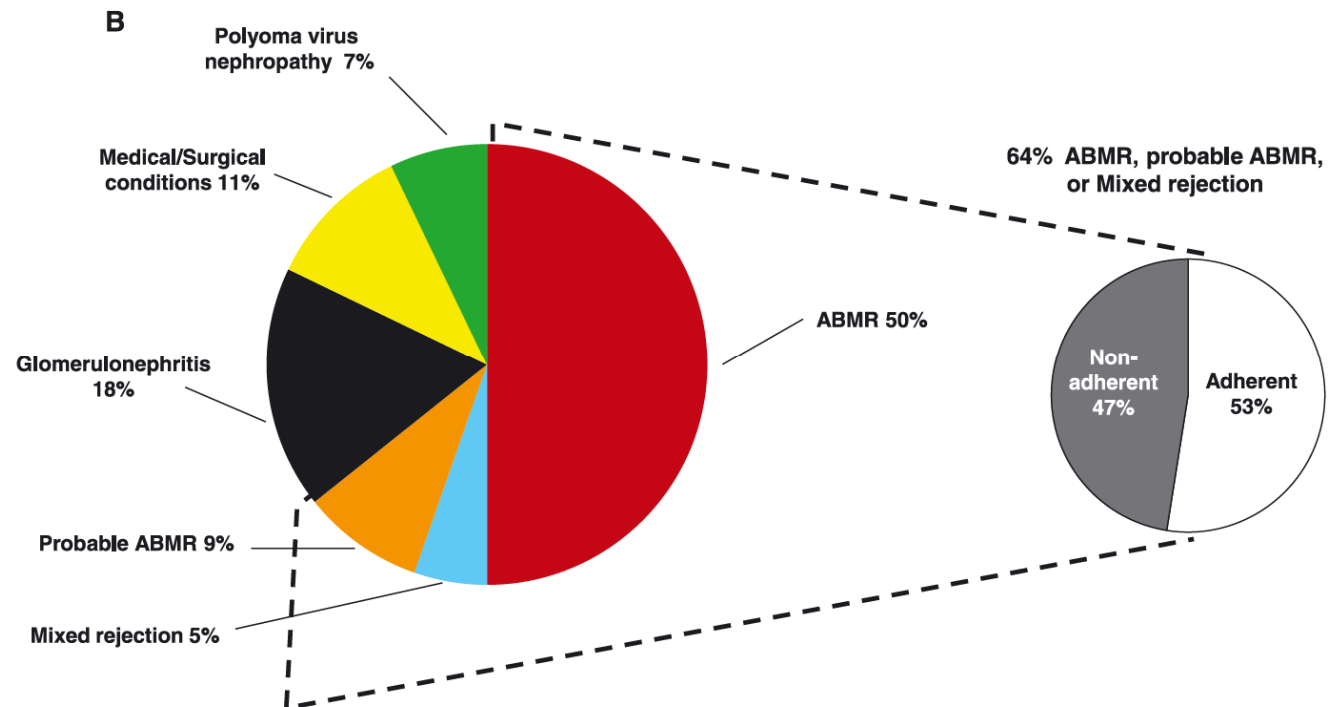
1. NTX ca. 15%
2. NTX ca. 65%
3. NTX ca. 85%
4. NTX ca. 95%

NACHTEILE VORSENSIBILISierter PATIENTEN

Prätrans- plant PRA	Wartezeit in Tagen
< 5%	788
61-84%	1.696
≥ 85%	2.232

ca. 1/3 vorsensibilisiert

URSACHEN DES TRANSPLANTATVERLUSTES



INTERVENTIONEN ZUR ANTIKÖRPERELIMINATION

Intravenöse Immunglobuline (IVIg)

Plasmapherese (PPh) + CMV Hyperimmunglobulin

Immunadsorption

+ / - T-Zell-depletierende Antikörper (ATG)

+ / - anti-CD20 Therapie (Rituximab)

+ / - Proteasomen-Inhibition (Bortezomib)

+ / - Komplement-Inhibition (Eculizumab)

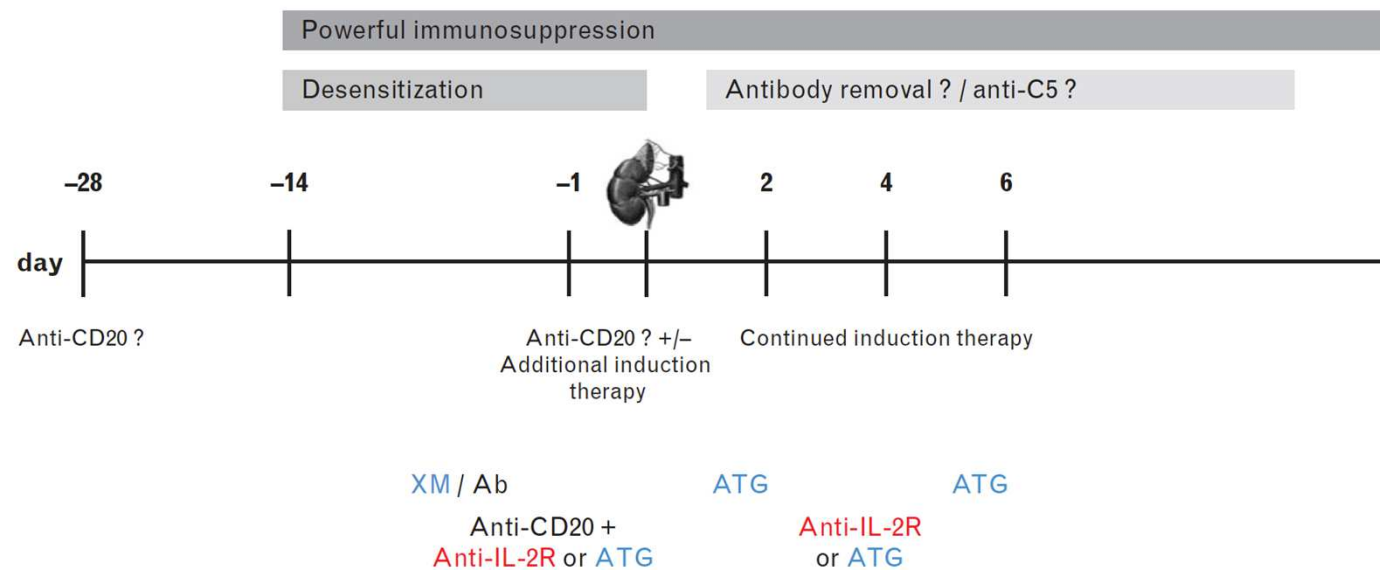
Splenektomie

Hemmung der Antikörperbildung

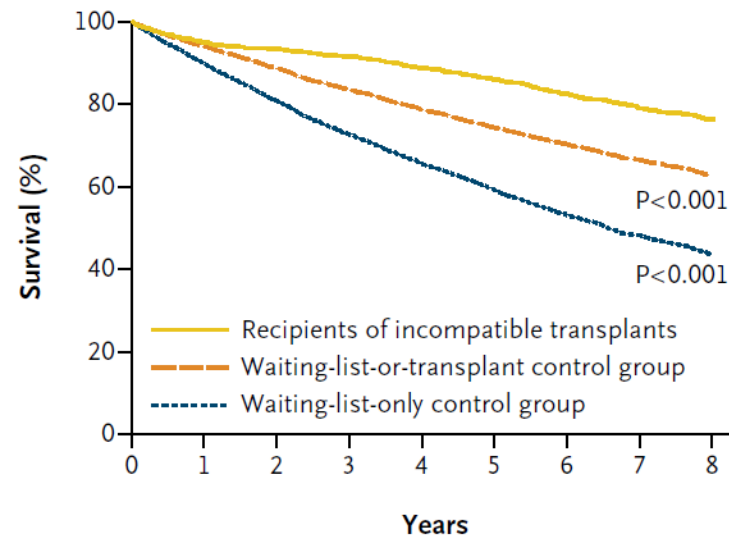
Entfernung von Antikörpern

Verschiedenes

DESENSITIZATION PROTOCOL

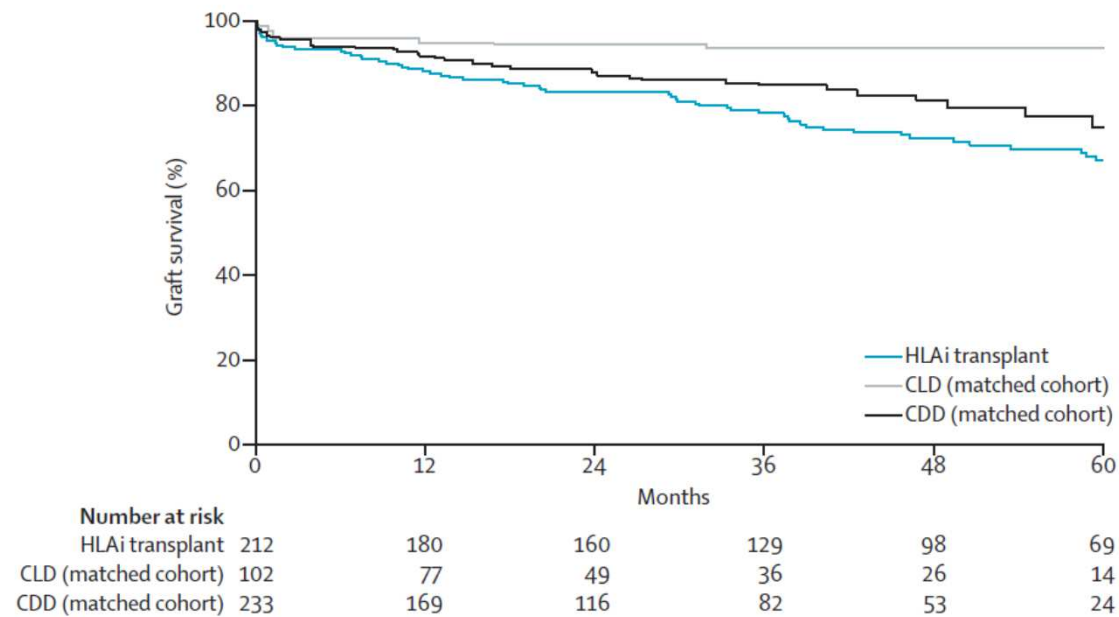


NTX DES VORIMMUNISIERTEN PATIENTEN



No. at Risk					
Recipients of incompatible transplants	1025	958	832	584	327
Waiting-list-or-transplant control group	5125	4546	3673	2493	1414
Waiting-list-only control group	5125	4141	3024	1810	916

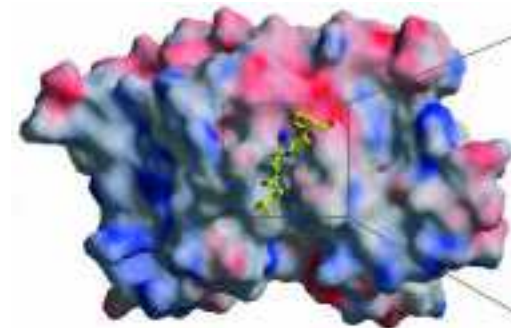
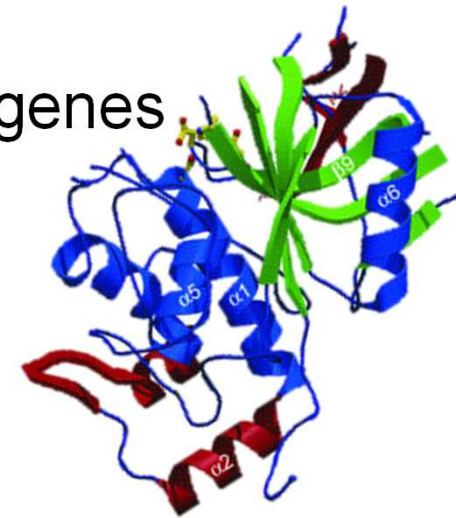
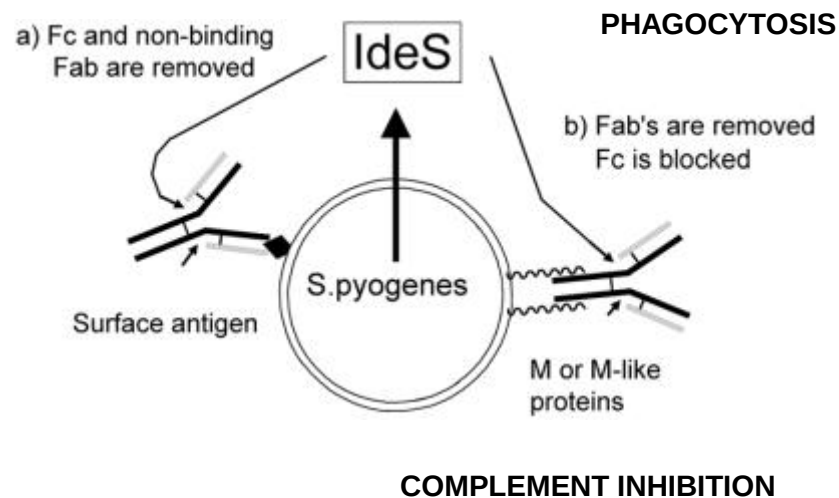
NTX DES VORIMMUNISIERTEN PATIENTEN



Manook M: Lancet 2017

IGG DEGRADING ENZYME OF STREP. PYOGENES

35 kDa Cystein Protease von Strep. pyogenes



WIRKSAMKEIT VON IDES

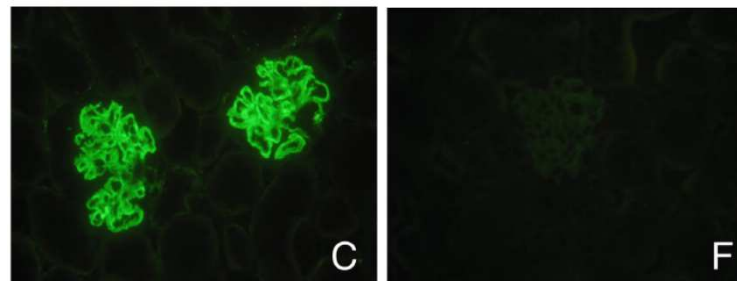
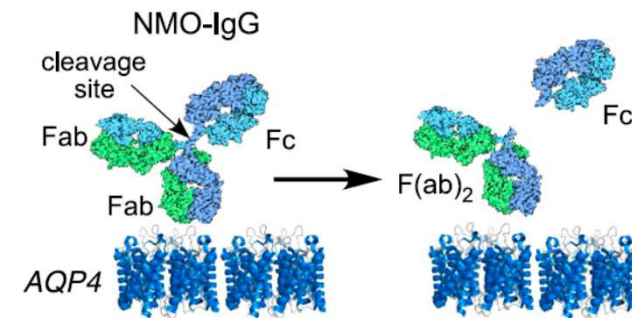
Rheumatoide Arthritis

ITP

Anti-GB-AK GN

Neuromyelitis optica (AQP4)

Guillain-Barré Syndrom

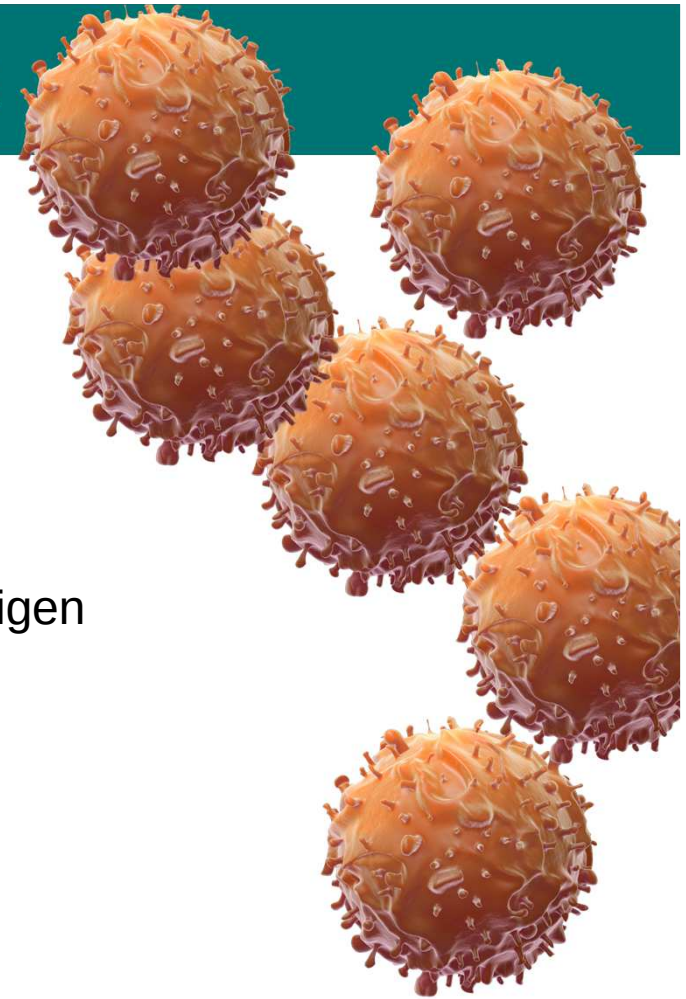
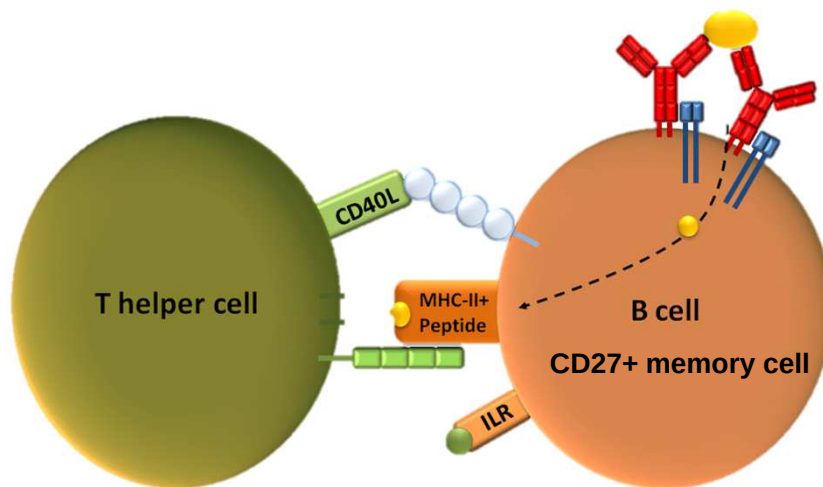


Nadakumar KS: Arthr Rheum 2007, Johansson BP: PLOS 2008,
Wang R: NDT 2010, Tradtrantip L: Mol Pharmacol 2013, Takahashi R: Scientific Rep 2015

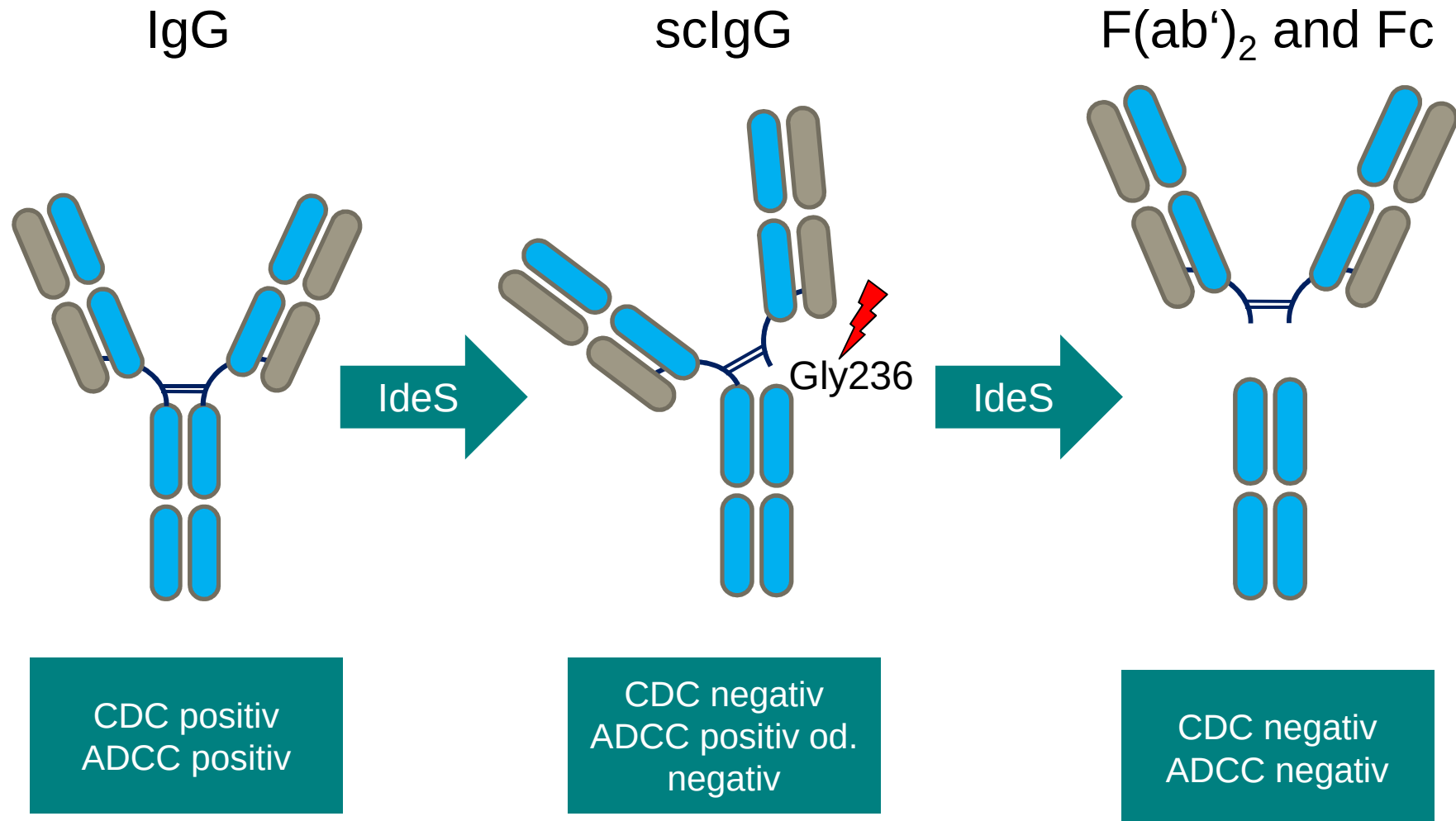
IGES SPALTET AUCH IgG B-ZELL REZEPTOR

Spaltung der BCR zirkulierender B-Zellen

- Inhibition der Antigen spezifischen B-Zell Antwort
- CDC
- ADCC
- Eingeschränkte Antwort der Memory Zellen auf Antigen

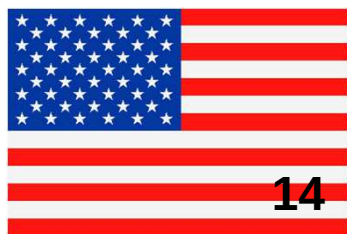
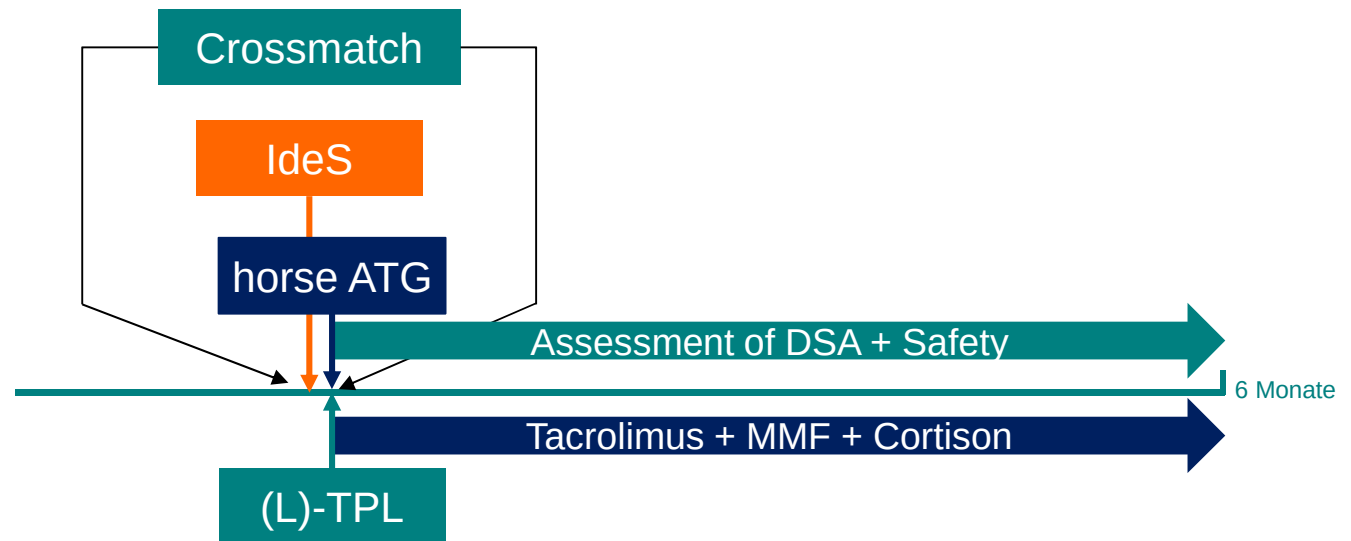


WIRKWEISE ENDOPEPTIDASE

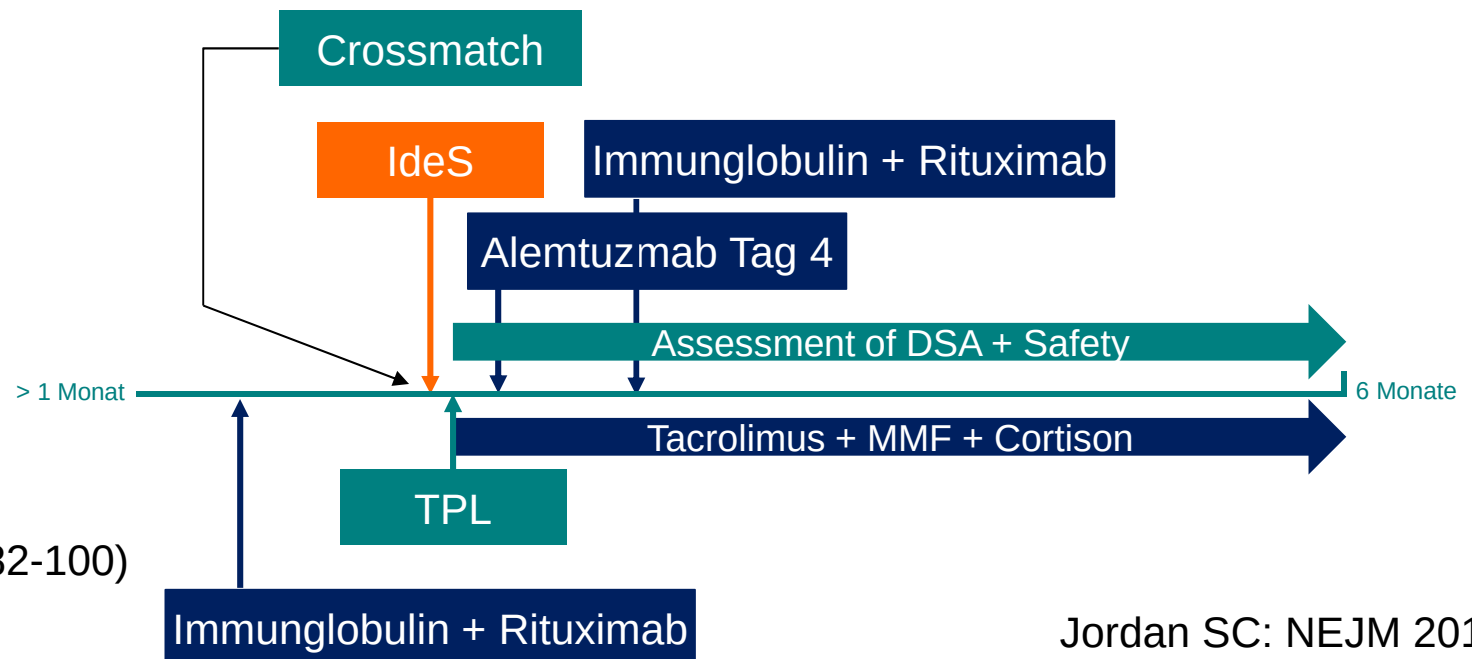




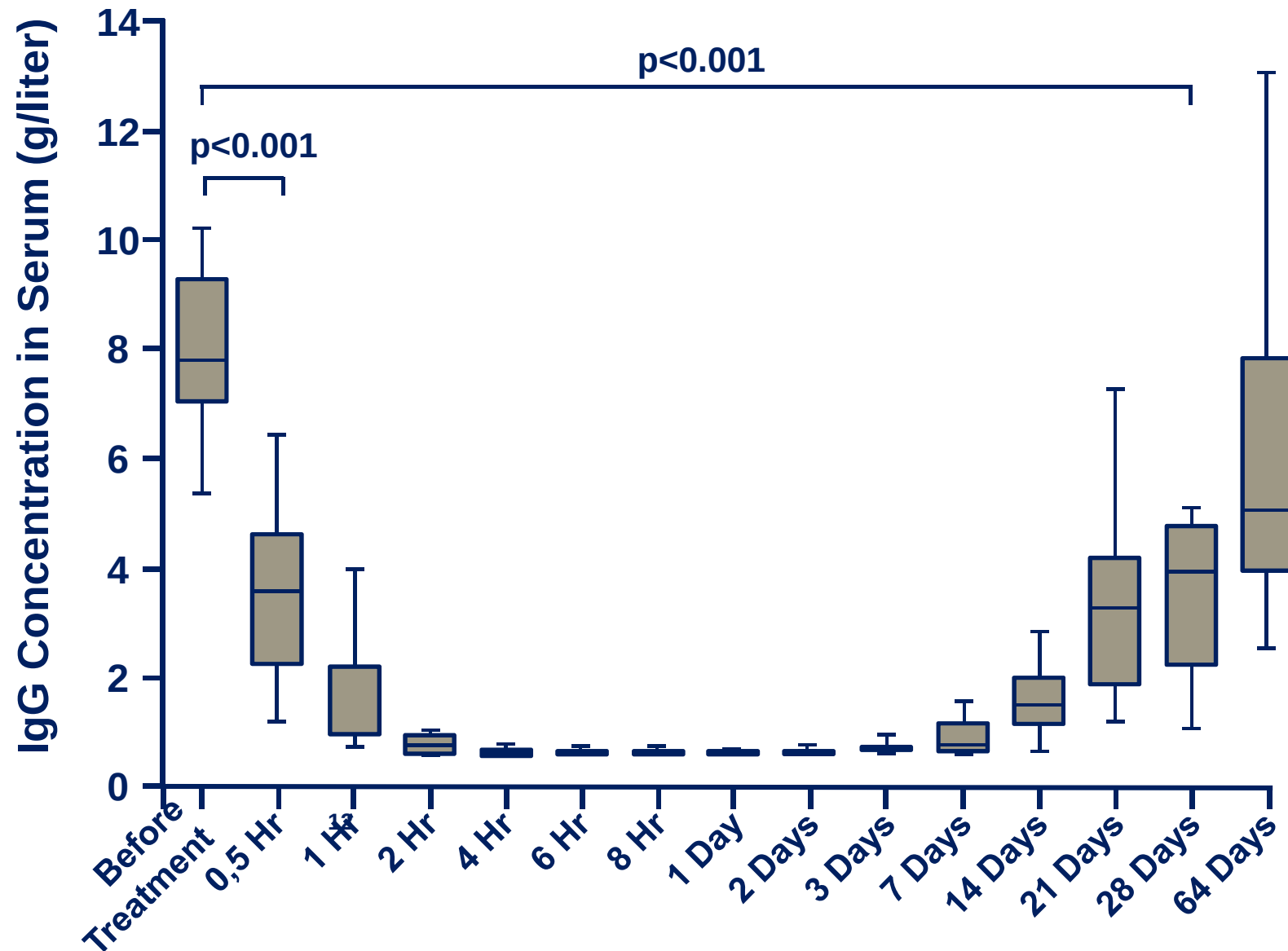
Median PRA 81% (22-100)



Median PRA 96% (82-100)

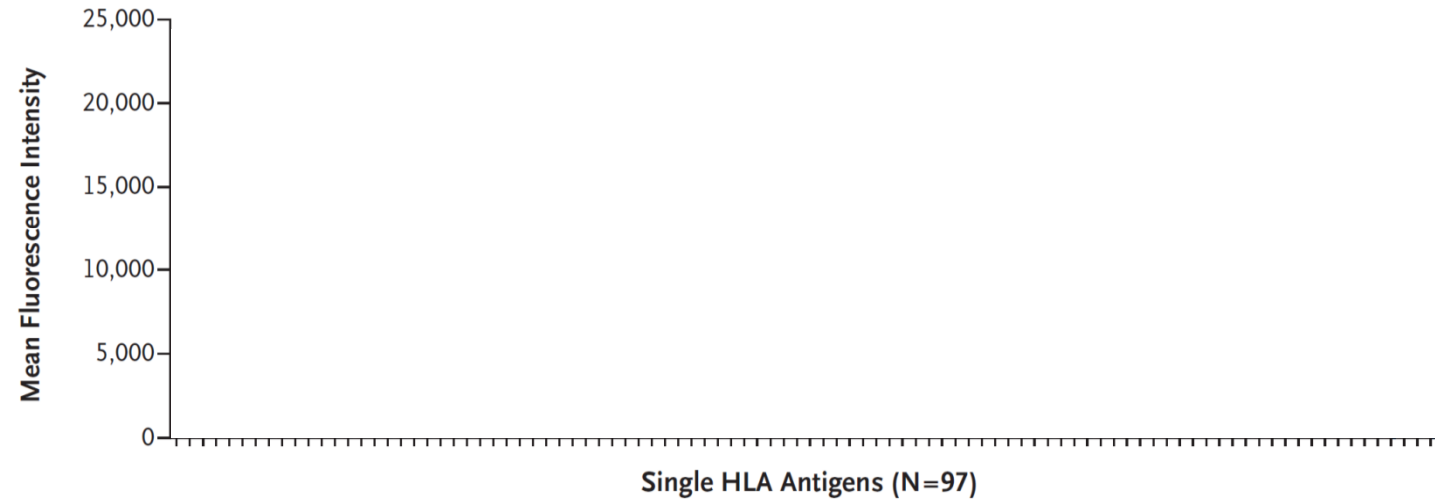


REDUKTION GESAMT-IgG

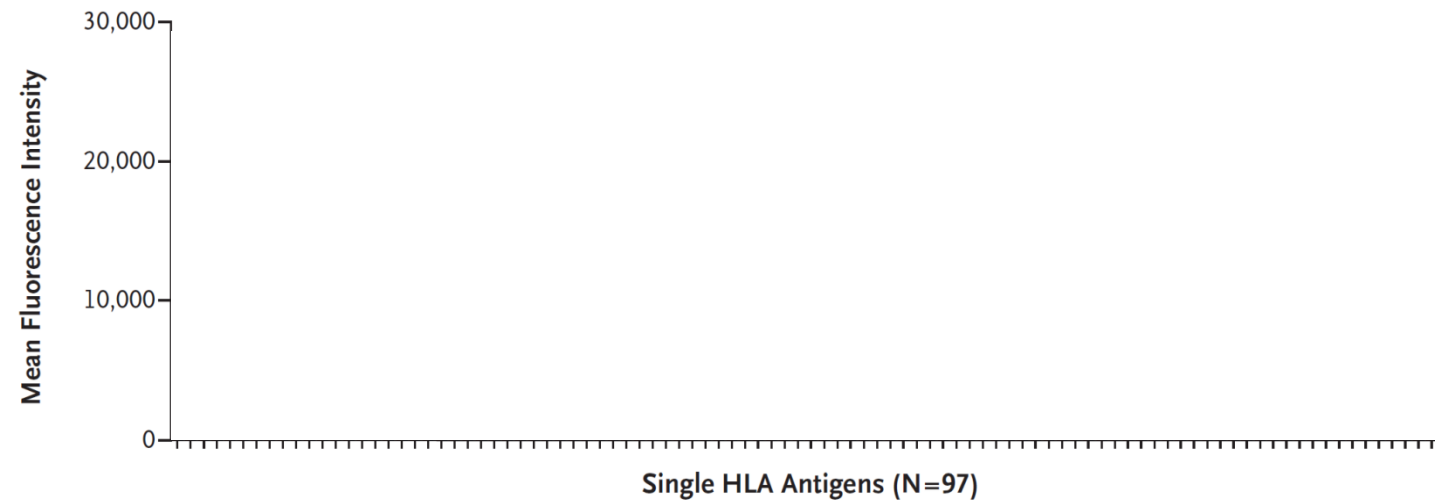


REDUKTION DER DSA

A HLA-Antibody Levels before and 6 Hr after Treatment



B C1q-Binding HLA-Antibody Levels before and 1 Hr after Treatment



PATIENTENCHARAKTERISTIKA

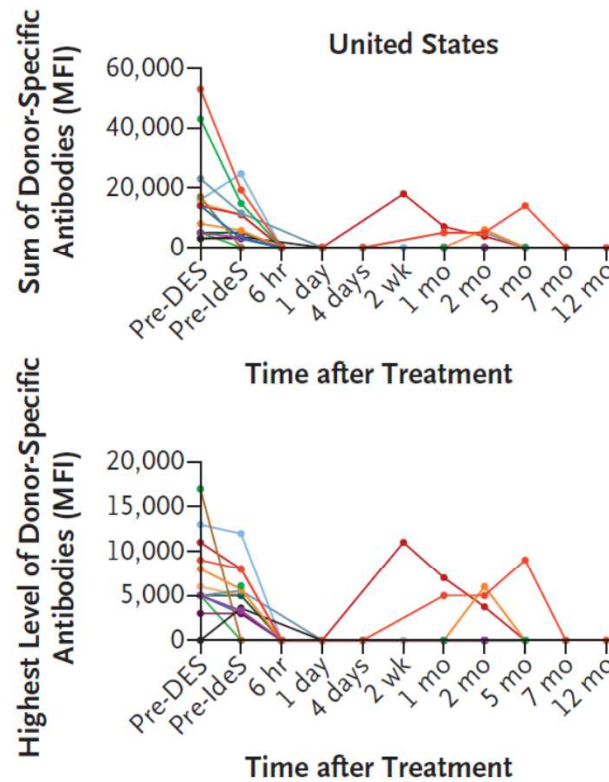
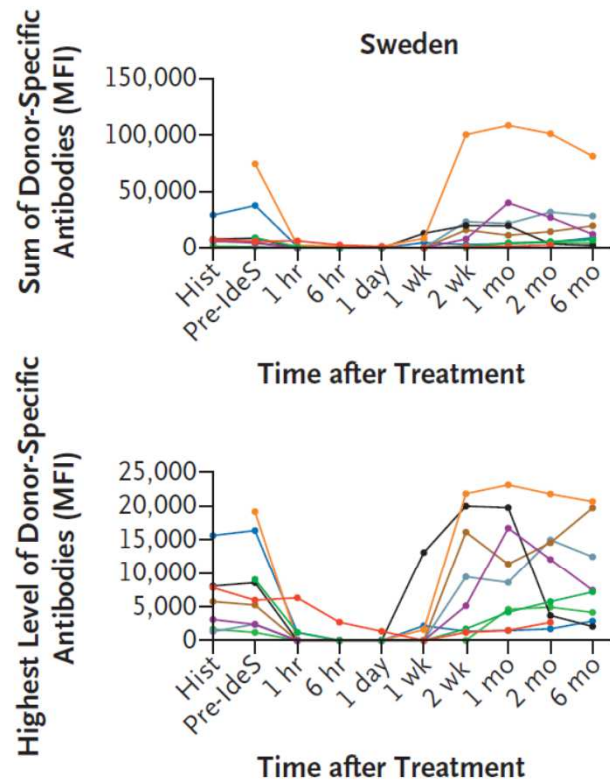
Characteristic	Total (N=25)	Sweden (N=11)	United States (N=14)	P Value
Recipient				
Age — yr	46.2±14	52.4±12.3	41.4±13.9	0.05
Male sex — no. (%)	11 (44)	4 (36)	7 (50)	0.69
At least 1 previous kidney transplant received — no. (%)	14 (56)	5 (45)	9 (64)	0.27

NEBENWIRKUNGEN

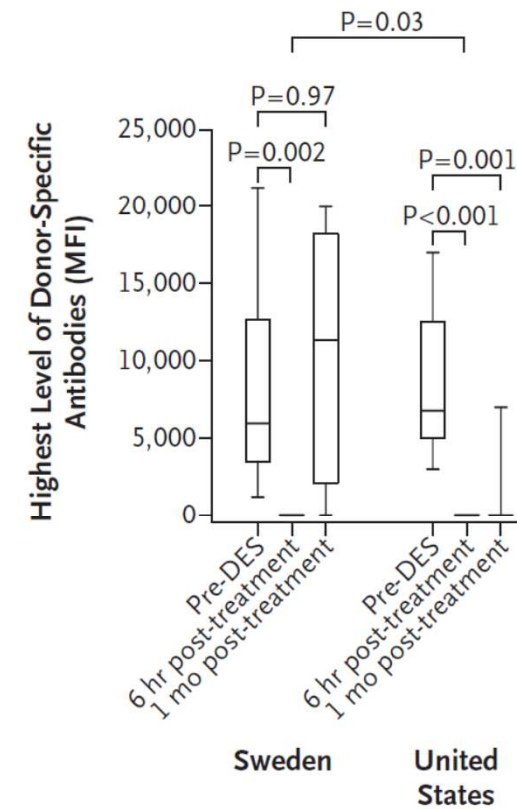
Event	No. of Events	Investigators' Assessment of Relatedness of Event to IdeS Treatment
Bacterial infection		
Urinary tract infection	5	Not related
Blood infection	3	Possibly related (in 1) and unlikely to be related (in 2)
Abdominal infection	1	Possibly related
Catheter-site infection	1	Possibly related
Pneumonia	2	Unlikely to be related (in 1) and not related (in 1)
Viral infection with parvovirus	1	Possibly related
Lymphocele	1	Not related
Renal-artery stenosis	1	Not related
Ureteric obstruction	2	Not related
Cholelithiasis or cholecystitis	2	Unlikely to be related (in 1) and not related (in 1)
Leukopenia	1	Not related
Elevated creatinine level	1	Not related
Rejection†		
Antibody-mediated rejection	5	Not related
Cell-mediated rejection	1	Not related
Both antibody-mediated rejection and cell-mediated rejection	2	Not related
Antibody-mediated rejection mediated by IgM antibody	1	Not related
Abdominal pain	3	Not related
Anemia	1	Not related
Fever	1	Not related
Atrial fibrillation and exacerbation of congestive heart failure	1	Not related
Malignant hyperthermia	1	Not related
Myalgia	1	Possibly related

KLINISCHE DATEN

A Donor-Specific-Antibody Levels in Individual Patients

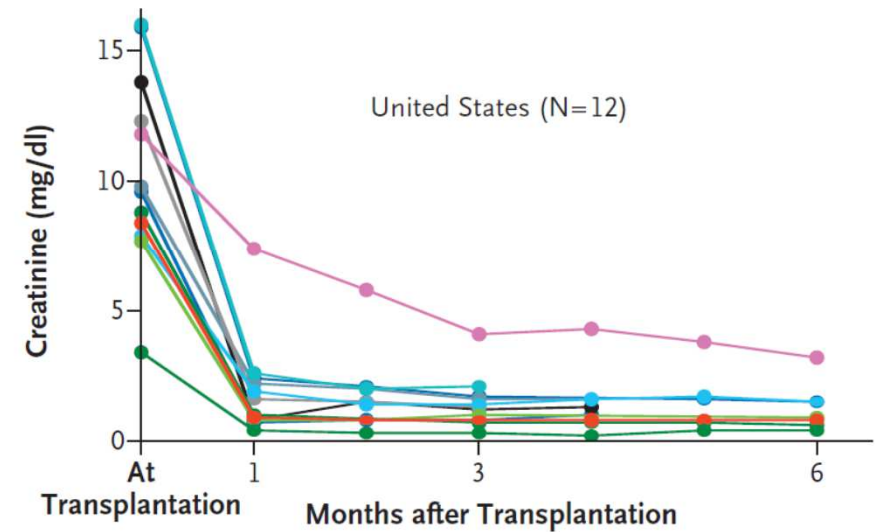
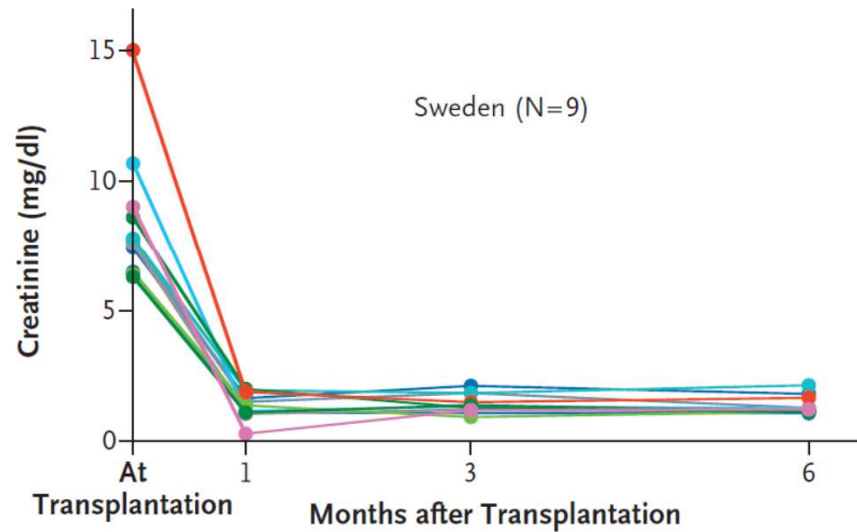


Median Highest Levels of Donor-Specific Antibodies

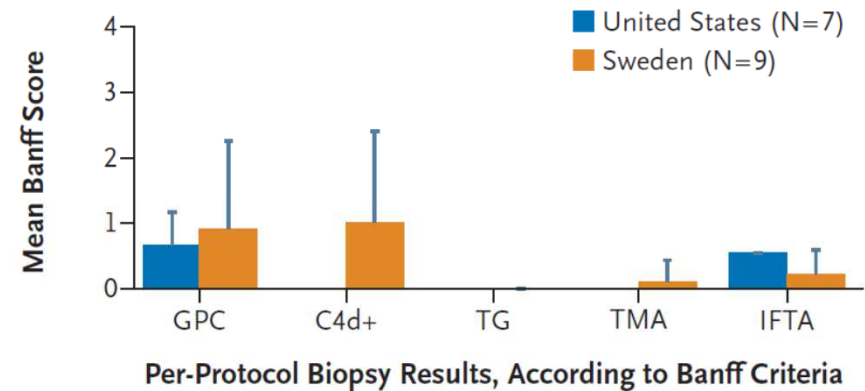
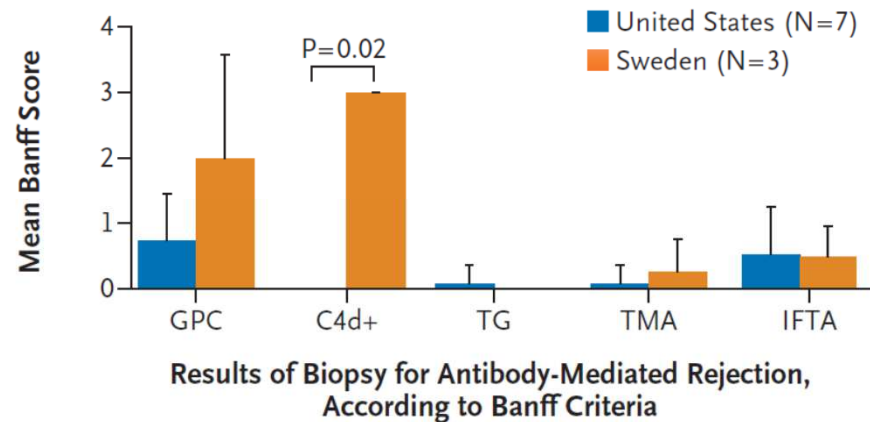


KLINISCHE DATEN

B Serum Creatinine Levels

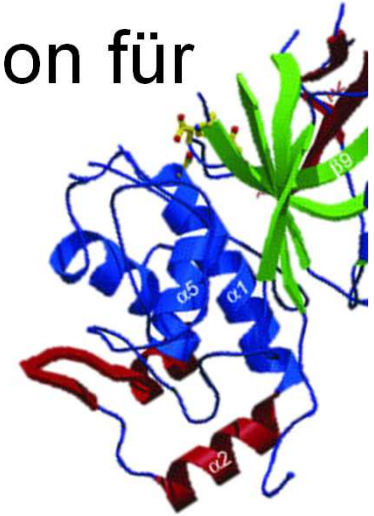


C Scoring of Biopsy Results



TAKE HOME MESSAGE

- IdeS sehr interessante neue Therapieoption für IgG vermittelte Erkrankungen
- Cave: IgG spezifisch (nicht IgM)
- bislang wenig Daten verfügbar
- Cave: Nebenwirkungsprofil
- Aphereseverfahren bald „überholt“?



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