



Treating anti-GBM disease with imlifidase

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Anti-GBM disease is a glomerulonephritis

- Glomerulonephritis (GN) is a group of inflammatory kidney diseases
- In GN the inflammation starts in the glomeruli
- GN is a leading cause of kidney disease necessitating renal replacement therapy (dialysis or transplantation)
- **Autoantibodies of IgG class can be found in most forms of GN (and in many other disease)**
- Anti-GBM disease is a model disease where autoantibodies have proven part in the disease process

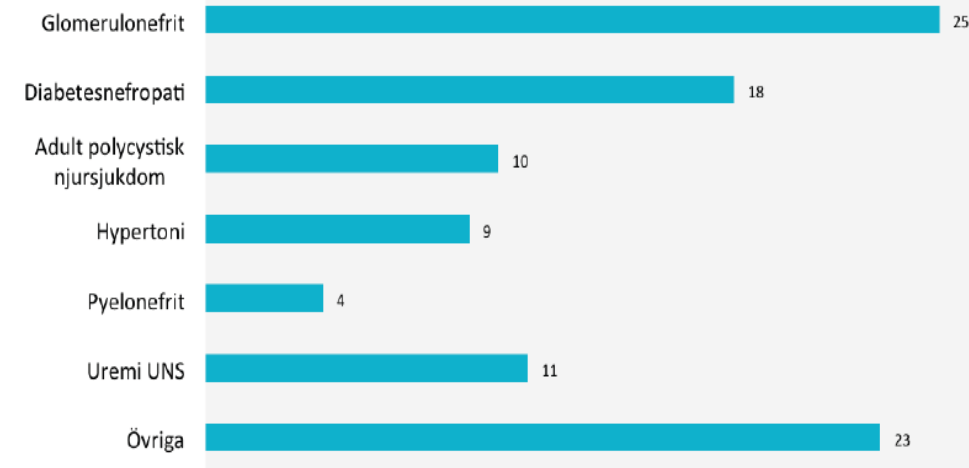
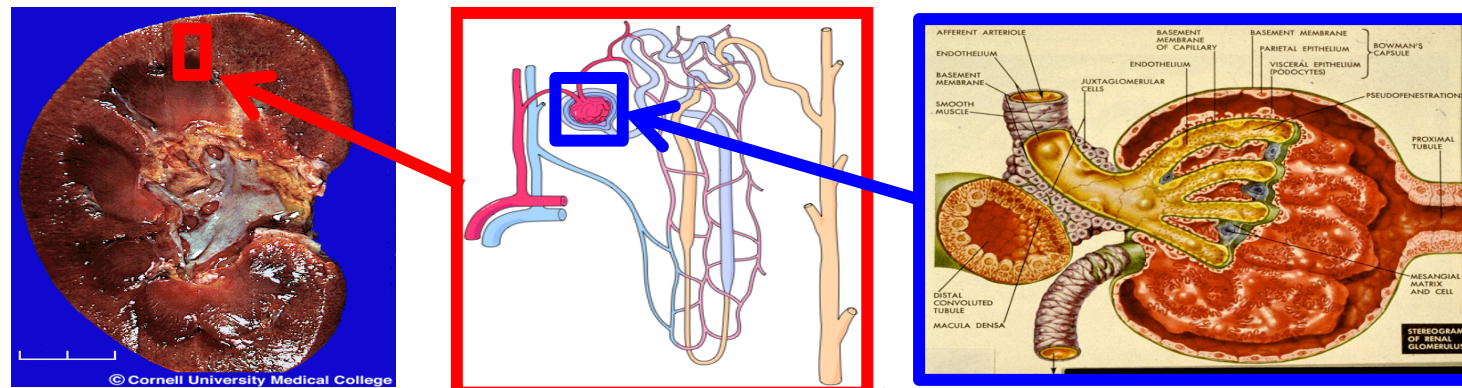


Fig 5. Uremiorsakande sjukdom. Samtliga patienter i aktiv uremivård 141231, i procent. n=9220

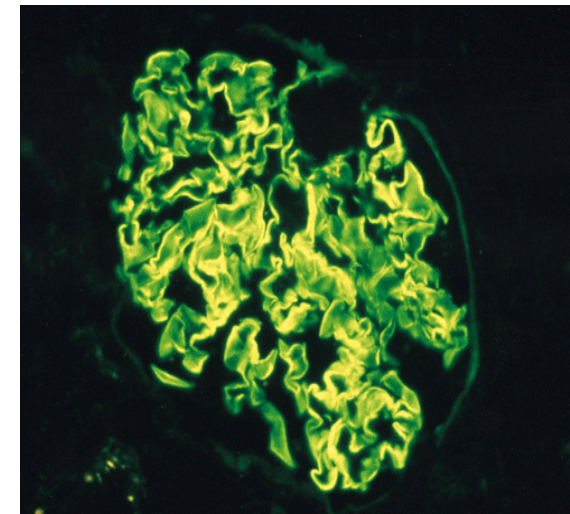


Anti-GBM disease – Goodpasture's disease

- Definition:
 - Renal and/or pulmonary disease caused by anti-GBM antibodies
- Unspecific symptoms for a few weeks (months)
- Rapidly progressive glomerulonephritis or acute renal failure
- Pulmonary hemorrhage (before GN, concomitant or late)
- Subclinical lung engagement – anemia, HRCT
- Incidence: 1.5 per million and year, men= women



Ernest William Goodpasture
1886-1960



Stanton and Tange. Australas Ann Med. 1958;7:132-44

Treatment of anti-GBM disease

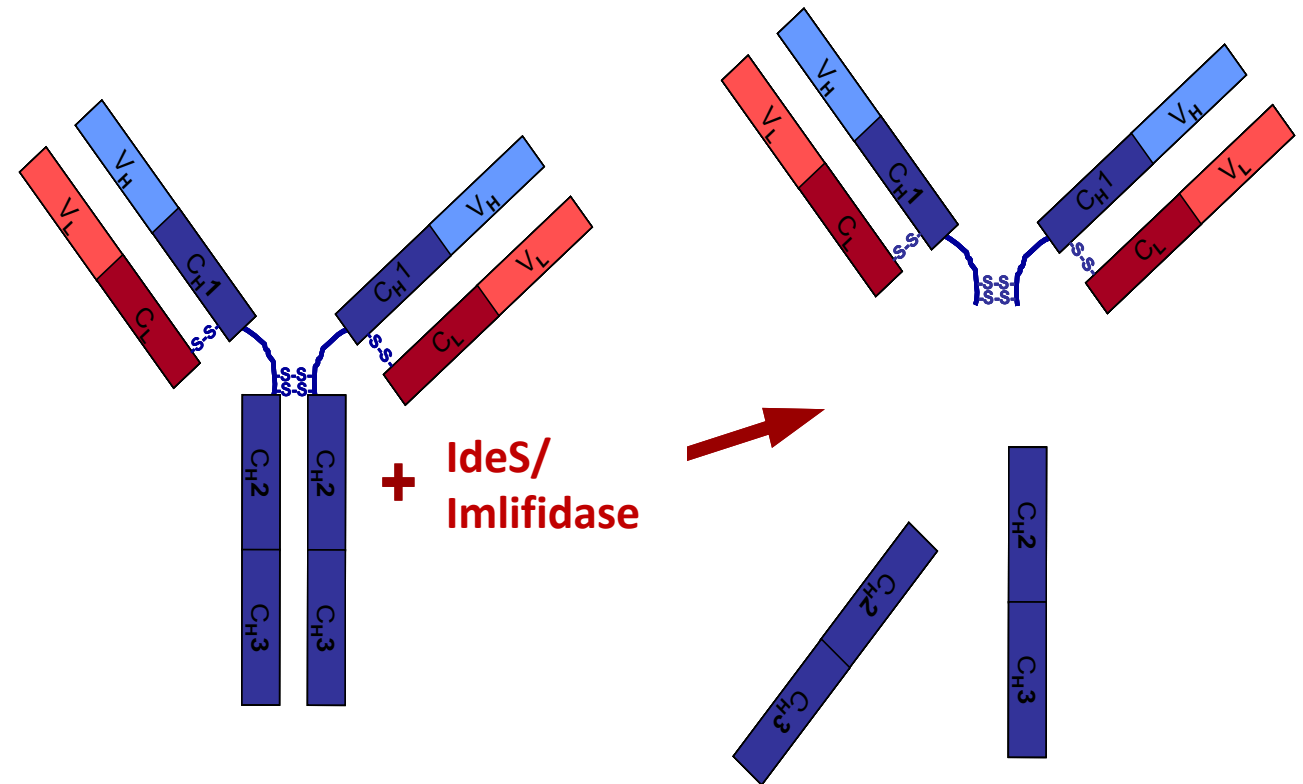
- Corticosteroids
- Cyclophosphamide
- Plasma exchange
- Supportive care as needed with dialysis and mechanic ventilation



Authors (year)	Country	Period	N	Dead at 6-12m	Native kidneys at 6-12 months		
					Total	If crea <5-600 at diagnosis	If dialysis/crea >5-600 at diagnosis
Herody et al 1993	France	1984-1992	29	2 (7 %)	12 (41 %)	12/13 (92 %)	0/16 (0 %)
Merkel et al 1994	Germany	1982-1992	35	4 (11 %)	10 (29 %)	9/14 (64 %)	1/21 (5 %)
Daly et al 1996	Ireland	1976-1991	40	3/34 (8 %)	8/34 (24 %)	8/14 (57 %)	0/20 (0 %)
Levy et al 2001	UK	1975-1999	71	15 (21 %)	29 (41 %)	18/19 (95 %)	11/52 (21 %)
Li et al 2003	Hong-Kong	1992-2003	10	2 (20 %)	2 (20 %)	2/6 (33 %)	0/4 (0%)
Segelmark et al 2003	Sweden	1987-1995	75	27 (36 %)	16 (21 %)	12/21 (53 %)	4/54 (7%)
Cui et al 2005	China	1997-2002	97	na	15 (15 %)	14/28 (50 %)	1/66 (2 %)
Taylor et al 2011	New Zealand	1998-2008	23	1(11 %)	11(48%)	na	na
Dammacco et al 2013	Italy	2003-2012	10	2 (20 %)	6 (60 %)	na	na
Zhang et al 2014	China	2003-2013	28	4 (14 %)	8 (20 %)	Na	Na
Alchi et al 2015	UK	1991-2011	43	5 (12 %)	10 (23 %)	6/8 (75 %)	2/35 (6 %)
Huart et al, 2016	France	1983-2006	122	16 (87%)	40/122 (33%)	33/50 (66%)	7/72 (10%)
MacAdoo et al 2017	UK, Sweden, Czech Rep	2000-2013	78	11/78 (14 %)	33/78 (42 %)	25/31 (81 %)	8/47 (17 %)
TOTAL			661	17% (76/442)	35% (200/576)	73 % (139/190)	9 % (34/373)

IdeS/Imlifidase = Immunoglobulin G degrading enzyme of *Streptococcus pyogenes*

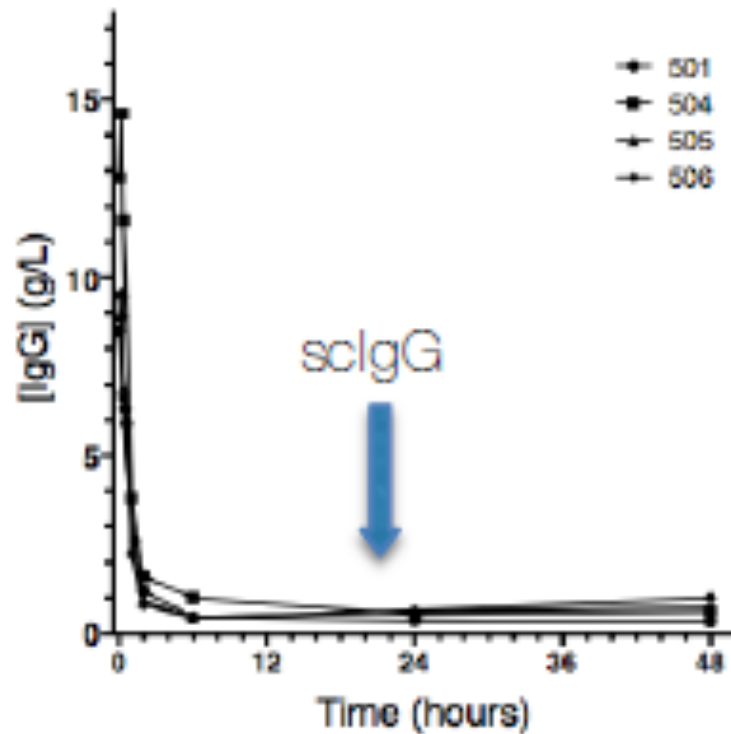
- Made by ordinary throat bacteria *S. pyogenes*
- Discovered by Lars Björck
- Effective in autoantibody mediated experimental models^{1,2}
- Developed to enable transplantation HLA-immunization³
- Official name as pharmacological substance = **imlifidase**



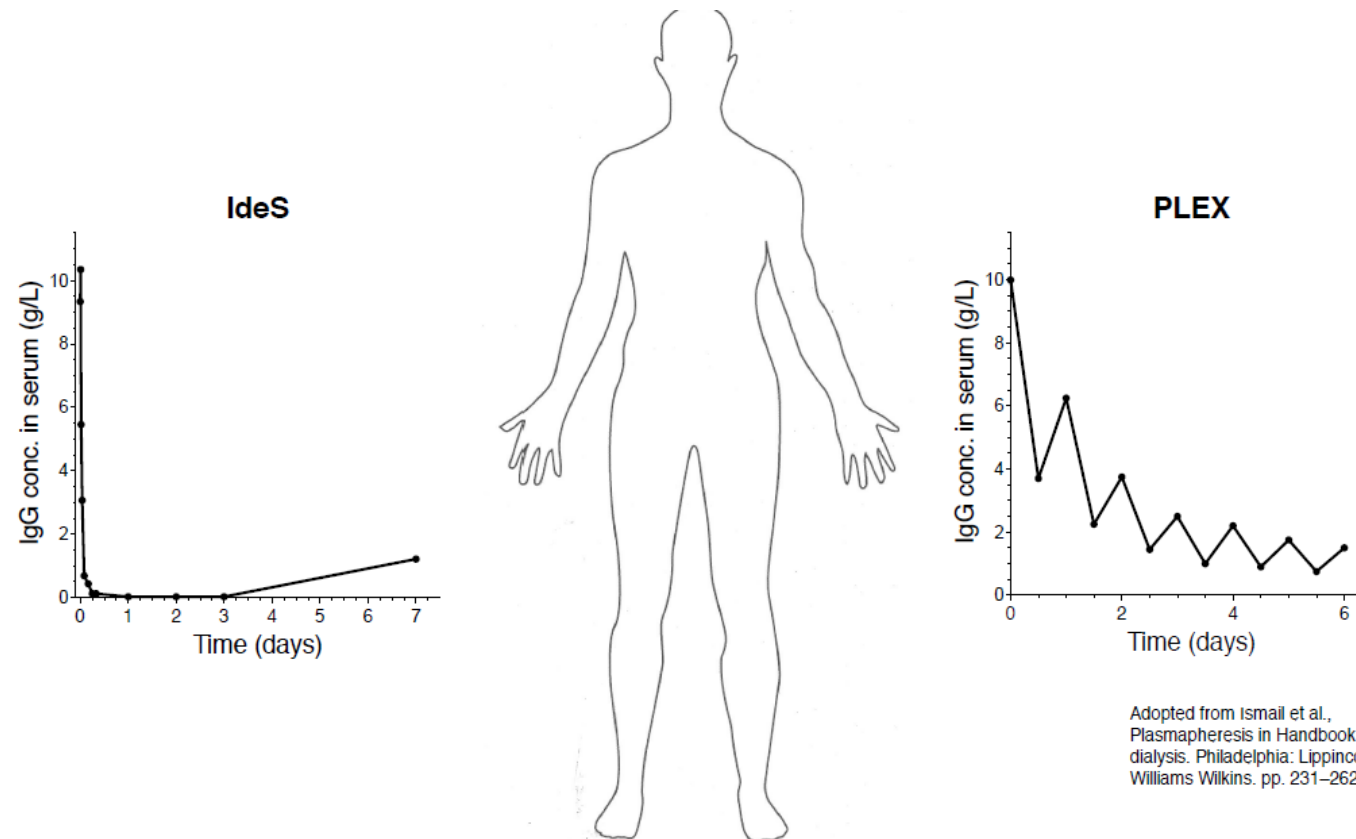
¹Johansson et al, PLoS ONE. 2008;3:1692. ²Nandakumar, Arthritis Rheum. 2007;56:3253-60.

³Jordan et al N Engl J Med. 2017 Aug 3;377(5):442-453

Cleaves all IgG in the body within 2-6 hours



To treat anti-GBM disease with imlifidase

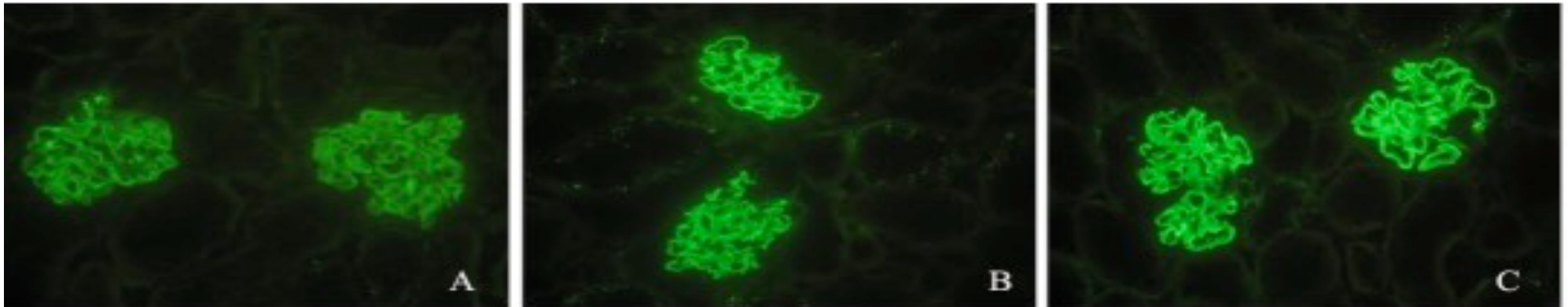


Adopted from Ismail et al.,
Plasmapheresis in Handbook of
dialysis. Philadelphia: Lippincott
Williams Wilkins. pp. 231–262.

Imlifidase can cleave IgG bound to mouse kidneys

- Mouse anti-rabbit IgG (Fc spec)

placebo



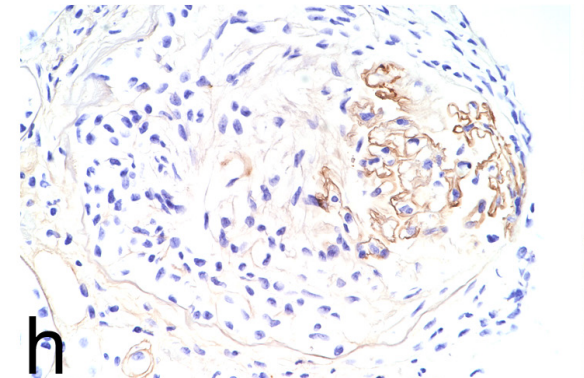
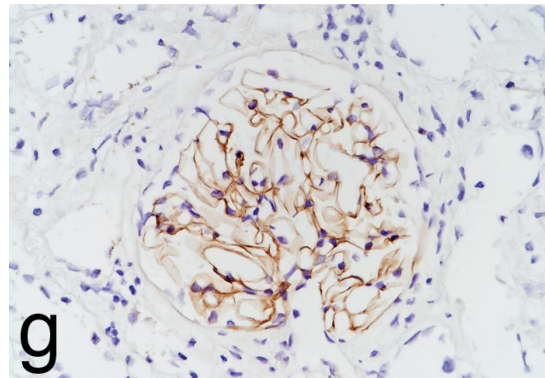
implifidase



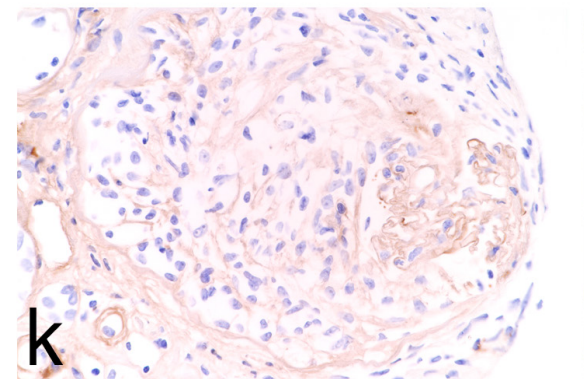
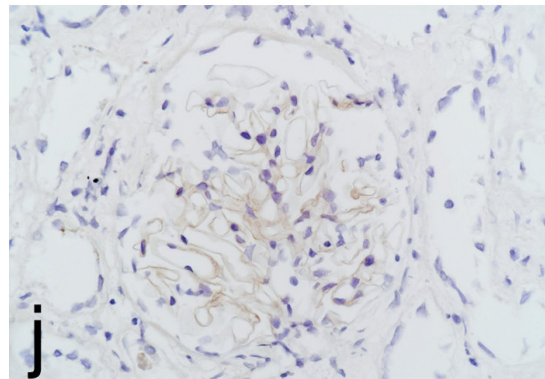
Compassionate treatment (3 patients)

Patient 1: 11 days after imlifidase Patient 2: 22 days after imlifidase

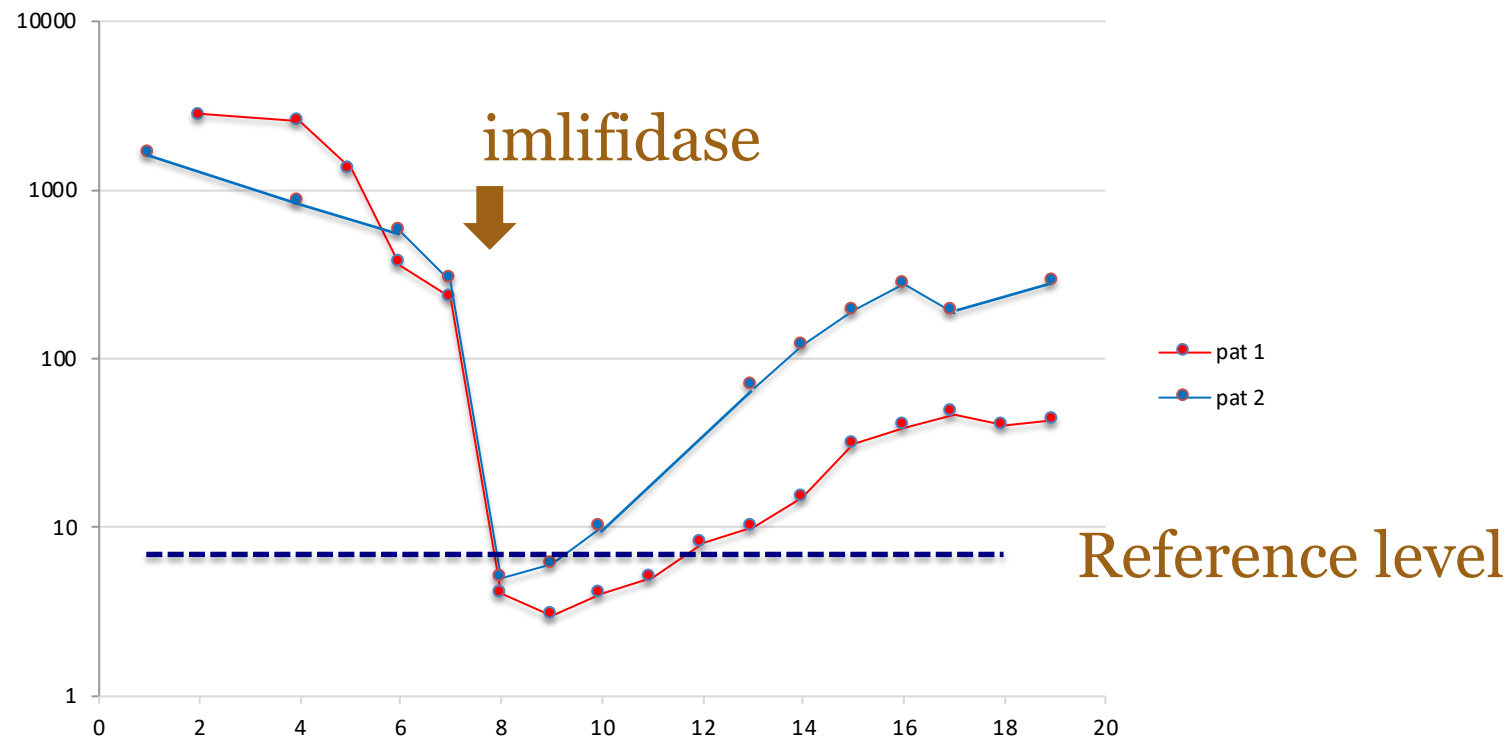
Anti-Fab₂-fragment



Anti-Fc-fragment



Compassionate treatment – anti-GBM levels



Soveri et al Kidney Int. 2019; 96:1234-1238

Investigator driven study: GOOD-IDES

- Open-label non-randomized multicenter study
- One dose of imlifidase on top of standard of care–
- 15 patients with bad prognosis (<15% of normal function)
- Total catchment area > 35 million
- 17 sites: 5 in **Sweden** 2 in **Denmark** , 4 in Austria, 1 in **Czech Republic**, 5 in **France**.

GOOD-IDES basal data

Renal function	Anuric	Dialysis but not anuric	eGFR<15	All
Number	5	5	5 (2 with failure on standard therapy)	15
F/M	1/4	1/4	4/1	6/9
Age (median/range)	72 (19-78)	60 (44-79)	61 (30-74)	61 (19-79)

Summary

- Anti-GBM disease is a prototype of autoantibody mediated diseases
- Autoantibodies are common in glomerulonephritis
- Anti-GBM is a rare GN, only 2 000 cases per year in Europe and North America
- With current therapy only 35% are alive with functioning kidneys six months after diagnosis
- Imlifidase cleaves anti-GBM within minutes, both in the blood and in the kidneys
- A phase II study has completed recruitment



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