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Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy after alemtuzumab therapy in kidney transplant recipients

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Alemtuzumab is approved for the treatment of relapsing-remitting MS and is used off-label for patients with chronic lymphocytic leukemia and as induction and antirejection therapy in kidney transplant recipients.[1] Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) complicating alemtuzumab treatment was reported in 9 patients with hematologic malignancy or MS.[1–3] The risk of GBS or CIDP in solid organ transplant recipients treated with alemtuzumab is unknown.

Rabbit antithymocyte globulin (rATG) is another T cell–depleting drug used to treat acute kidney allograft rejection. Only 1 patient was reported who developed GBS after rATG treatment for aplastic anemia.[4] We found no reports of GBS or CIDP complicating rATG treatment in kidney transplant recipients. Here, we investigated the frequency, type, and outcome of GBS and CIDP in a single-center cohort of kidney transplant recipients treated with either alemtuzumab or rATG.

Methods

Study design

A retrospective analysis was performed of a cohort of kidney transplant recipients who received either alemtuzumab (Campath, Sanofi-Genzyme, Cambridge, MA) or rATG (Thymoglobulin, Sanofi-Genzyme) between 2002 and 2018 in the Erasmus MC, Rotterdam. Alemtuzumab was administered as a single dose of 30 mg subcutaneously and rATG in a dose of 4 mg/kg and nog g/kg.

Statistical methods

Continuous variables are presented as median and interquartile ranges (IQRs). The 95% CIs were calculated with the modified Wald method. For statistical analysis, SPSS version 21 (SPSS Inc., Chicago, IL) was used.

Standard protocol approvals, registrations, and patient consents

The study was approved by the Erasmus MC Medical Ethical Review Board (number 2018-1430).

Results

Between 2002 and 2018, 2,788 patients received a kidney transplant at our center. Alemtuzumab was administered to 143 (5.1%) patients and rATG to 108 (3.9%) patients. The total follow-up period of patients treated with alemtuzumab was 3.0 years (IQR 1.7–4.1 years) for

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Table Clinical characteristics, diagnosis, and outcome of patients with GBS and CIDP after alemtuzumab

Case	1 (GBS)	2 (GBS)	3 (CIDP)
Sex	Male	Female	Male
Age at onset symptoms (y)	54	57	63
Primary kidney disease	Polycystic kidney disease	Reflux nephropathy	Polycystic kidney disease
CMV status at transplantation	Seropositive	Seronegative	Seropositive
Induction therapy	Alemtuzumab (30 mg, 30 days before transplantation, IVIg 0.4 g/kg on the day of transplantation), immunoabsorption	Basiliximab	Basiliximab
Antirejection therapy	None	Alemtuzumab (30 mg)	Alemtuzumab (30 mg)
Immunosuppressive treatment at onset symptoms	Tacrolimus/MMF/prednisolone 5 mg/d	Tacrolimus/MMF/prednisolone 2.5 mg/d	Tacrolimus/MMF/prednisolone 5 mg/d
Diagnosis	GBS, level 2 of Brighton classification (no electrophysiologic studies available)	GBS (AIDP), level 1 of Brighton classification	CIDP (fulfillment of clinical criteria and definite electrophysiologic criteria EFNS/PNS 2010)
Interval between alemtuzumab treatment and symptoms (mo)	4	8	42
Onset to maximum severity (d)	21	10	90
Maximum mRS score (range 0–6)	4	5	4
Maximum GBS disability score (range 0–6)	4	5	—
EGOS (range 0–7)	3.5	6.5	—
Treatment	IVIg (0.4 g/kg) for 5 days	IVIg (0.4 g/kg) for 5 days	2× IVIg (0.4 g/kg) for 5 days, 4 sessions of plasma exchange, methylprednisolone (3× 1000 mg), prednisone 5 mg daily (maintenance)
mRS score after treatment	1	6	1
GBS disability score after treatment of GBS	1	6	—
Neurologic outcome at the last follow-up	Partial recovery (follow-up 1 year)	Death (6 months later, due to malignancy)	Full recovery (follow-up 3 years)

Abbreviations: AIDP = acute inflammatory demyelinating polyradiculoneuropathy; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; EGOS = Erasmus GBS Outcome Score; GBS = Guillain-Barré syndrome; IVIg = IV immunoglobulin; MMF = mycophenolate mofetil; mRS = modified Rankin Scale.

a total of 444.3 person-years. A tacrolimus-based immunosuppressive regimen was given to 92% of patients. Three patients (2.1%, 95% CI 0.4%–6.3%) developed GBS or CIDP after alemtuzumab. Two patients fulfilled the diagnostic criteria for GBS, and 1 fulfilled the diagnostic criteria for CIDP. The clinical presentation and diagnostic findings of these patients are presented in the table. Laboratory tests, including clinical chemistry, serology, and virology, demonstrated no alternative diagnoses, and there was no recent *Campylobacter jejuni* or cytomegalovirus infection (PCR negative for cytomegalovirus). The total follow-up period for rATG-treated patients was 8.2 (IQR 6.3–11) years for a total of 829.4 person-years. Seventy-eight percent of patients received a tacrolimus-based immunosuppressive regimen. None of the patients treated with rATG (0%, 97.5% CI 0–4.1%) developed GBS or CIDP.

Discussion

This study shows that 2.1% of patients treated with alemtuzumab developed GBS or CIDP. This is higher than the incidence rate of these neuropathies in the general population and of kidney transplant recipients not treated with alemtuzumab.[5–7] Secondary autoimmunity after alemtuzumab appears to be mainly B cell driven. A mismatched reconstitution of T and B cells after alemtuzumab can lead to an expansion of B cells in the absence of appropriate T-cell regulation. This may enable the escape of autoreactive B cells and production of pathogenic autoantibodies to self-antigens, which can lead to secondary autoimmunity, such as thyroiditis, idiopathic thrombocytopenic purpura, GBS, or CIDP.[1]

None of the patients treated with rATG developed GBS or CIDP. A possible explanation for the difference in the risk of developing these neuropathies with alemtuzumab is that the depletion of immune cells lasts longer after alemtuzumab.[1] Alternatively, rATG may protect from GBS and CIDP.

Limitations of the current study are that we were unable to define the frequency of GBS and CIDP in kidney transplant recipients not treated with T cell–depleting therapy. Second, no causality between alemtuzumab and the risk of GBS or CIDP was demonstrated, and our findings may therefore relate to chance. Third, cytomegalovirus could have played a role in the development of GBS or CIDP because patients 1 and 3 were seropositive for cytomegalovirus at the time of transplantation. However, no signs of a reactivation were observed at the time the patients were diagnosed with GBS and CIDP. Fourth, we cannot exclude that the increased incidence of GBS and CIDP among alemtuzumab-treated patients may relate to the fact that in this group, more patients used tacrolimus as maintenance immunosuppression compared with the rATG cohort. Fifth, this observation is based on kidney transplant recipients who have several reasons to have an underlying neuropathy (i.e., renal insufficiency and diabetes mellitus), and it is uncertain whether it is also applicable to patients with MS.

In conclusion, alemtuzumab therapy in kidney transplant recipients may be associated with the development of GBS and CIDP. Clinicians should be alert for these neurologic complications in kidney transplant recipients treated with alemtuzumab.

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Name	Location	Contribution
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