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Clinical Research Article

Prevalence, Risk Factors, and Clinical and Biochemical Characteristics of Alemtuzumab-Induced Graves Disease

Grethe Åstrøm Ueland,[1] Hans Olav Ueland,[2] Ann-Elin Meling Stokland,[3] Alok Bhan,[4] Anne Schønberg,[1] Stina T. Sollid,[5] Dina Edvarda Morgas,[6] Trygve Holmøy,[7,8] Kari Lima,[9] Paal Methlie,[1,10] Kristian Løvås,[1] Øivind Torkildsen,[10,11] and Eystein S. Husebye[1,10]

[1]Department of Medicine, Haukeland University Hospital, 5021 Bergen, Norway
[2]Department of Ophthalmology, Haukeland University Hospital, 5021 Bergen, Norway
[3]Department of Endocrinology, Stavanger University Hospital, 4019 Stavanger, Norway
[4]Department of Neurology, Stavanger University Hospital, 4019 Stavanger, Norway
[5]Department of Medicine, Drammen Hospital, Vestre Viken Health Trust, 3004 Drammen, Norway
[6]Department of Ophthalmology, Drammen Hospital, Vestre Viken Health Trust, 3004 Drammen, Norway
[7]Department of Neurology, Akershus University Hospital, 1478 Oslo, Norway
[8]Institute of Clinical Medicine, University of Oslo, 0313 Oslo, Norway
[9]Department of Medicine, Akershus University Hospital, 1478 Oslo, Norway
[10]Department of Clinical Medicine, University of Bergen, 5009 Bergen, Norway
[11]Department of Neurology, Neuro-SysMed, Haukeland University Hospital, 5021 Bergen, Norway

Correspondence: Grethe Åstrøm Ueland, MD, PhD, Department of Medicine, Haukeland University Hospital, Jonas Lies vei 65, 5021 Bergen, Norway. Email: geas@helse-bergen.no

Abstract

Objective: Atypical Graves disease (GD) is a common complication in multiple sclerosis (MS) patients treated with alemtuzumab. We present epidemiological, clinical, and biochemical characteristics of alemtuzumab-induced GD.

Methods: Retrospective follow-up study of MS patients treated with alemtuzumab from 2014 to 2020, including clinical course of GD, pregnancy outcome, and thyroid eye disease (TED).

Results: We enrolled 183 of 203 patients (90%, 68% women) treated with alemtuzumab at 4 hospitals in Norway. Seventy-five (41%) developed thyroid dysfunction, of whom 58 (77%) had GD. Median time from the first dose of alemtuzumab to GD diagnosis was 25 months (range, 0-64). Twenty-four of 58 GD patients (41%) had alternating phases of hyper- and hypothyroidism. Thyrotropin receptor antibodies became undetectable in 23 of 58 (40%) and they could discontinue antithyroid drug treatment after a median of 22 (range, 2-58) months. Conversely, 26 (44%) had active disease during a median follow-up of 39 months (range, 11-72). Two patients (3%) received definitive treatment with radioiodine, 6 (10%) with thyroidectomy. Nine developed TED (16%), 7 had mild and 2 moderate to severe disease. Four patients completed pregnancy, all without maternal or fetal complications. Patients who developed GD had a lower frequency of new MS relapses and MRI lesions than those without.

Conclusion: GD is a very common complication of alemtuzumab treatment and is characterized by alternating hyper- and hypothyroidism. Both remission rates and the prevalence of TED were lower than those reported for conventional GD. Pregnancies were uncomplicated and GD was associated with a lower risk of subsequent MS activity.

Key Words: Graves disease, autoimmune thyroid disease, thyroid eye disease, alemtuzumab, multiple sclerosis

Abbreviations: ATD, antithyroid drug treatment; CAS, Clinical Activity Score; FDA, Food and Drug Administration; EDSS, Expanded Disability Status Scale; EUGOGO, European Group of Graves' Orbitopathy; FT4, free thyroxine; GD, Graves disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; TED, thyroid eye disease; TPOAb, thyroid peroxidase antibodies; TRAb, thyrotropin receptor autoantibodies; TSH, thyrotropin (thyroid-stimulating hormone).

Alemtuzumab is a humanized monoclonal antibody that targets the cell membrane protein CD52, expressed on the surface of more than 95% of all B and T lymphocytes in peripheral blood. It mediates lytic destruction with rapid and prolonged depletion of these cells from the circulation (1). Since 2015, alemtuzumab has been widely used to treat relapsing-remitting multiple sclerosis (MS) in adults. In 2018, the U.S. Food and Drug Administration (FDA) issued a warning that rare but serious cases of stroke had occurred in some MS patients shortly after receiving alemtuzumab (2). The warning led to limited use of alemtuzumab from 2020, despite good treatment effects of MS (3).

Alemtuzumab is administered intravenously in 2 cycles 12 months apart. In the cases where there is insufficient treatment response, a third cycle can be given (4). Autoimmune thyroid dysfunction, and in particular Graves disease (GD), is the most common side effect of alemtuzumab, with reported frequencies of 30% to 40% (5-7). GD usually develops several years after treatment, with a peak 2 to 3 years after the first dose. Several reports indicate that alemtuzumab-induced

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GD has an atypical presentation compared with conventional GD, often characterized with high levels of thyrotropin receptor autoantibodies (TRAb), and a fluctuating and unpredictable disease course with rapid oscillations between hyper- and hypothyroidism (5, 6, 8). However, reports on disease outcomes are conflicting (1, 8, 9). Some patients experience a surprisingly mild burden of symptoms relative to TRAb levels and thyroid hormone abnormalities. Moreover, it seems that the occurrence of complications such as thyroid eye disease (TED) is low, but there are limited data to support this claim (8). Given that patients treated with alemtuzumab often are young, fertile female individuals, there is a lack of data on pregnancy risks posed by high and fluctuating TRAb levels.

The purpose of this study was to provide a comprehensive description of alemtuzumab-induced GD, including disease course, remission rate, TED, and pregnancy outcome in a representative Norwegian population. Furthermore, we aimed to explore any potential differences between MS patients who developed GD after alemtuzumab treatment and those who did not.

Methods

Study Population

We identified all patients with MS treated with alemtuzumab at 4 large hospitals in Norway, from the introduction of alemtuzumab treatment in 2015 until the end of December 2022. During this period, a total of 203 MS patients received alemtuzumab at these hospitals, and 183 (90%) consented to participate in the study. Data were obtained from the patient records.

Definitions and Clinical Data

Data on sex, age, smoking habits, work ability, duration of MS, type of thyroid dysfunction (if present), concomitant autoimmune diseases, autoantibodies, thyroid status, and treatment modalities were obtained from medical records. In addition, remission rates and pregnancy outcomes were obtained.

All patients had thyroid function testing monthly after the first dose of alemtuzumab. Thyroid-stimulating hormone (TSH) or free thyroxine (FT4) levels outside the reference range prompted measurement of free triiodothyronine (FT3), thyroid peroxidase antibody (TPOab) and TRAb.

Thyroid dysfunction was defined as an abnormal TSH level on 2 or more occasions, at least 3 months apart (6). Subclinical hypothyroidism was defined as TSH greater than the upper reference limit for the assay, with FT4 within the reference range. Overt hypothyroidism was defined as TSH greater than the reference range and FT4 below the reference range. Subclinical hyperthyroidism was defined as TSH below the reference range and FT4 within the reference range, and overt hyperthyroidism as TSH below the reference range and FT4 above the reference range. GD was defined as the presence of subclinical or overt hypo- or hyperthyroidism, with positive TRAb (10, 11). Autoimmune thyroiditis was characterized as an initial phase of thyrotoxicosis, followed by spontaneous hypothyroidism or euthyroidism, and negative TRAb. Patients were categorized as having TED according to current clinical guidelines (12). All patients with suspected TED were examined by a dedicated ophthalmologist and classified according to the European Group of Graves' Orbitopathy (EUGOGO)'s classification (12). Inflammatory activity was assessed by Clinical Activity Score (CAS) (13). Active TED was defined as a CAS score of 3 (or higher) out of 7.

Patients who were euthyroid without medication for at least 1 year were defined as being in remission from GD. The end of follow-up was set to March 3, 2023.

Autoantibodies

TRAb and TPOAb levels were analyzed as part of clinical routine at local hospitals. For TRAb, 3 of the 4 centers used electrochemiluminescence immunoassay (ECLIA) (Roche Cobas®, Mannheim, Germany) (Roche Cat# 04 388 780 190, RRID:AB_2801453). At one hospital, Phadia 2500 (Thermo Fisher Scientific Cat# MA3-218, RRID: AB_325488) was used. Eight patients had their TRAb measured by this method. Because of different analytical methods, local reference ranges were used to determine the presence or absence of these autoantibodies.

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (SPSS Version 26.0; IBM Corporation, Armonk, NY, USA). Categorical data are reported as absolute numbers and percentages, while continuous data are reported as median (range). Differences between groups were evaluated using the Chi-square test and Mann-Whitney U test, as appropriate. A two-tailed P value $<.05$ was considered statistically significant.

Ethics

The Regional Committee for Medical and Health Ethics of Western Norway approved the study protocol, and all participants gave written informed consent (REK number 79348).

Results

Clinical and Epidemiological Characteristics

A total of 183 patients with MS treated with alemtuzumab (90%) were included in the study (Table 1). Median follow-up time from the first dose of alemtuzumab to the end of study was 72 (48-109) months. Twenty patients did not sign the informed consent, either because they did not want to participate or because they were unavailable. Before treatment with alemtuzumab was started, 19 patients (10.4%) had one ($n = 17$) or more ($n = 2$) autoimmune diseases in addition to MS, including autoimmune hypothyroidism ($n = 7$), type 1 diabetes ($n = 5$), and celiac disease ($n = 5$). Thirteen patients (7.1%) had a first-degree relative with autoimmune disease.

The MS Disease

The median age at diagnosis of MS was 30.5 (10-61) years. The most common treatment regimens given before alemtuzumab were fingolimod (41%) and interferon beta-1a and -1b (41%) (Table 2). The median duration of MS before the first dose of alemtuzumab was 5 (0-33) years, and at this time point the Expanded Disability Status Scale (EDSS) score was 2.5 (0-8). A second dose of alemtuzumab was given to 173 patients (94.5%), and 19 patients (10.4%) received a third dose. Improvement of EDSS score was observed in 67 patients (36.6%), whereas a decline was found in 34 patients (18.6%). At the end of the follow-up period, 48 patients (26.2%) had

Table 1. Patient characteristics and autoimmune comorbidity

Parameter	Total study population ($n = 183$)	GD ($n = 58$)	Other thyroid autoimmunity ($n = 17$)	No thyroid autoimmunity ($n = 108$)	*P* value[b]
Women, *n* (%)	124 (67.8%)	49 (84.5%)	14 (82.3%)	61 (56.5%)	<.001
Age (years), median (range)	45 (22-73)	40 (28-60)	51 (32-66)	46 (22-73)	.021
Weight (kg), median (range)	72 (46-143)	72 (46-143)	72 (52-124)	74.4 (48-119)	.26
Height (cm), median (range)	172 (157-196)	170 (157-187)	170 (159-186)	172 (157-196)	.08
BMI (kg/m^2), median (range)	24.1 (18-47)	24.8 (18-47)	23.5 (19-43)	23.5 (18-43)	.87
Nicotine habits,					
Current smoker	18 (9.8%)	8 (13.8%)	1 (5.9%)	9 (8.3%)	.09[c]
Nonsmoker	145 (79.2%)	47 (81.0%)	12 (70.6%)	86 (79.6%)	
Former smokers	20 (10.9%)	3 (5.2%)	4 (23.5%)	13 12.0%)	
E-smokers	2 (1.1%)	0 (0%)	0 (0%)	2 (1.9%)	.41
Snuff	10 (5.5%)	3 (5.2%)	1 (5.9%)	6 (5.6%)	.17
Employment status					
Full-time	42 (23.0%)	16 (27.6%)	2 (11.8%)	24 (22.2%)	.24[d]
Part-time	38 (20.8%)	12 (20.7%)	5 (29.4%)	21 (19.4%)	
Not working	78 (42.6%)	24 (41.4%)	8 (47.0%)	46 (42.6%)	
Unknown	25 (13.7%)	6 (10.3%)	2 (11.8%)	17 (15.7%)	
Autoimmunity					
Autoimmune comorbidity, n (%)	19 (10.4%)	9 (15.5%)	0 (0%)	10 (9.3%)	.21
- Thyroid disease before alemtuzumab, n (%)[a]	7 (3.8%)	2 (3.4%)	0 (0%)	5 (4.6%)	
- Type 1 diabetes mellitus, n (%)	5 (2.7%)	2 (3.4%)	0 (0%)	3 (2.8%)	
- Celiac disease, n (%)	5 (2.7%)	2 (3.4%)	0 (0%)	3 (2.8%)	
- Other autoimmune comorbidity	4 (2.2%)	2 (3.4%)	0 (0%)	2 (1.9%)	
Number of autoimmune diseases, median (range)	0 (0-2)	0 (0-2)	0	0 (0-1)	
Autoimmune heritage present	13 (7.1%)	4 (6.9%)	0 (0%)	9 (8.3%)	.82
- Heritage for thyroid disease	2 (1.1%)	1 (1.7%)	0 (0%)	1 (0.9%)	
- Heritage for other autoimmune diseases	11 (6.0%)	3 (5.2%)	0 (0%)	8 (7.4%)	

Abbreviations: BMI, body mass index; GD, Graves disease.
[a]Six patients had Hashimoto thyroiditis, one was operated for GD with total thyroidectomy prior to alemtuzumab treatment. It is noted in the table how many cases with preexisting thyroid disease developed addition thyroid dysfunction after alemtuzumab treatment.
[b]*P* values represent comparison between patients that developed GD, and those who did not develop thyroid autoimmunity.
[c]*P* value represents comparison of current smokers and nonsmokers.
[d]*P* value represents comparison of patients working full-time or part-time, and patients not working.

experienced a new MS relapse, and new magnetic resonance imaging (MRI) lesions were found in 54 patients (29.5%).

Thyroid Dysfunction

Out of 183 included patients, 75 (41%) developed thyroid dysfunction. Among them, 58 (77%) had GD, 9 (15.8%) had autoimmune thyroiditis, 3 (5.7%) had subclinical hyperthyroidism with negative TRAb, and 5 patients (6.7%) had other types of thyroid dysfunction not further classified. The median time from the first dose of alemtuzumab to the development of thyroid disease was 25 (0-69) months.

Characteristics of the Patients With GD

Of the 183 patients treated with alemtuzumab, 58 (32%) developed GD. Of these patients 33 were hyperthyroid, one was hypothyroid, and the remaining 24 had switching thyroid function. One case had concurrent GD and autoimmune thyroiditis. Biochemical data for thyroid hormones at diagnosis are presented in Table 3. More women than men developed GD (40% vs 15%; odds ratio 3.9; CI, 1.6-9.5) (Fig. 1). Due to a limited number of smokers, valid calculations regarding the effect of smoking habits were not feasible.

Twenty-three patients (40%) turned seronegative for TRAb and discontinued antithyroid drug treatment (ATD) after a median time of 22 (2-58) months. No relapses were observed even though 19 had been without ATD for more than 12 months. Conversely, 26 (44.8%) patients had active disease after a median follow-up time of 39 (11-72) months. Two patients received radioiodine treatment, 9 and 15 months after the onset of GD, respectively, and 7 patients underwent thyroidectomy after a median time of 33 (30-55) months.

The presence of GD did not appear to have negative impact on working ability (Table 1). No associations were found between the development of GD and the duration of the MS disease, the presence of autoimmune comorbidities, the age at MS diagnosis, or the age when alemtuzumab treatment was started. None of the previous treatment regimens for MS were associated with higher risk of developing GD.

Table 2. Clinical characteristics and treatment of the multiple sclerosis

Parameter	Total study population ($n = 183$)	GD ($n = 58$)	Other thyroid autoimmunity ($n = 17$)	No thyroid autoimmunity ($n = 108$)	*P* value[a]
Age at MS diagnosis (years), median (range)	30.5 (10-61)	28 (17-53)	38 (26-61)	31 (10-59)	.17
Duration of the MS disease before alemtuzumab (years), median (range)	5 (0-33)	4 (0-19)	8 (0-24)	6 (0-33)	.25
EDSS score at 1 alemtuzumab treatment, median (range)	2.5 (0-8)	2.5 (0-7)	2 (1-6)	2.5 (0-8)	.58
Alemtuzumab dose 2 administered, n (%)	173 (94.5%)	55 (94.8%)	14(82.4%)	104 (96.3%)	.64
Alemtuzumab dose 3 administered, n (%)	19 (10.4%)	5 (8.6%)	3 (17.6%)	11(10.2%)	.47
MS attacks after alemtuzumab, n (%)	48 (26.2%)	10 (17.2%)	5 (29.4%)	33(30.5%)	.11
Improved EDSS score after alemtuzumab, n (%)	67 (36.6%)	22 (37.9%)	8 (47%)	37 (34.3%)	.85
Declined EDSS score after alemtuzumab, n (%)	34 (18.6%)	10 (17.2%)	3 (17.6%)	21 (19.4%)	.72
Development of new MRI lesions after alemtuzumab, n (%)	54 (29.5%)	10 (17.2%)	4 (23.6%)	40 (37.0%)	.009
MS treatment prior to alemtuzumab, n (%)					
Interferon beta 1a and 1b	75 (41%)	23 (39.7%)	7 (41.2%)	45 (41.6%)	.80
Glatiramer acetate	61 (33.3%)	17 (29.3%)	8 (47.1%)	36 (33.3%)	.56
Teriflunomide	30 (16.4%)	5 (8.6%)	3 (17.6%)	22 (20.3%)	.05
Dimethyl fumarate	40 (21.9%)	18 (31%)	5(29.4%)	17 (15.7%)	.021
Natalizumab	72 (39.3%)	27 (46.6%)	7(41.2%)	38 (35.2%)	.15
Cladribine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0
Fingolimod	75 (41.0%)	19 (32.8%)	8(47.1%)	48 (44.4%)	.07
Ocrelizumab	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0
Rituximab	1 (0.5%)	1 (1.7%)	0 (0%)	0 (0%)	.17

Abbreviations: EDSS, Expanded Disability Status Scale; GD, Graves disease; MRI, magnetic resonance imaging; MS, multiple sclerosis.
[a]*P* values represent comparison of patients that developed GD with those that did not develop thyroid autoimmunity.

Patients who developed GD after alemtuzumab treatment had lower frequency of new MS attacks, and significantly fewer new MS lesions on MRI (17.2 vs 35.2%, $P < .0001$) compared with those who did not develop GD.

A total of 56 patients (31%) who received alemtuzumab were subsequently started on other disease-modifying drugs for MS. Of these, 38 received rituximab. Six of these patients developed alemtuzumab-induced GD, and at the end of the follow-up, 1 of these 6 patients was able to terminate ATD, and 1 patient underwent thyroidectomy 9 months after the onset of GD.

Thyroid Eye Disease

TED was observed in 9 of 58 patients (15.5%) after a median of 40.5 (18-41) months following alemtuzumab treatment and 17 (10-49) months following the diagnosis of GD. The median CAS was 1 (0-3) at diagnosis; 7 had mild and 2 had moderate to severe TED. None had sight-threatening disease (12). Six patients were treated with artificial tear drops, 1 with selenium and 2 with oral glucocorticoids. No patient required reconstructive surgery. Of the 9 patients with TED, 2 of the 9 had received radioiodine treatment prior to the development of TED (2 and 21 months before, respectively), and 1 was still on ATD treatment after 22 months.

Pregnancy

Four patients became pregnant while having active GD. Of these 4 patients, 3 had TRAb levels at least 3 times the upper reference limit throughout pregnancy, of whom 2 patients received thyroxine throughout pregnancy and 1 patient was treated with propylthiouracil in the first trimester. The fourth patient was treated with propylthiouracil until pregnancy, and no treatment thereafter. Her TRAb normalized during the first trimester. All patients were euthyroid during pregnancy. The children were all born to term, and no thyroid abnormalities or other malformations were detected in the fetuses or neonates.

Discussion

We here present a cohort of 183 patients with MS who were receiving alemtuzumab treatment, covering 90% of all patients treated with the drug at 4 hospitals in Norway over

a 7-year period. The results corroborate that thyroid dysfunction, particularly GD, is a frequent complication of alemtuzumab treatment (5, 6). Our study identified a substantially higher prevalence of fluctuating GD activity than previously reported (5, 6). Compared with conventional GD, a longer duration of ATD treatment was necessary, but surprisingly, no relapses were detected after treatment discontinuation and the rate of GD-related complications was low.

Our finding that 41.4% of GD patients exhibit fluctuation between hyper- and hypothyroid state is significantly higher than the 17% previously reported (5, 6). This is a crucial finding, since the rapid shifts make treatment challenging and may result in uncontrolled hyper- or hypothyroidism, even in patients who adhere strictly to treatment and follow-up routines. Our results thus support current clinical guidelines that recommend monthly thyroid function testing and long-term follow-up for MS patients treated with alemtuzumab to enable prompt detection and timely referral to an endocrinologist, if needed (14). Usually, a titrating ATD regimen is chosen for GD patients at our institutions, but in 12 of the 58 GD patients, a block and replacement treatment regimen was used. For 9 of these patients, the regimen was chosen because of fluctuating thyroid levels, and for the remanding 3, it was because of TED. The high incidence of fluctuating thyroid states also supports the liberal use of block-and-replace treatment.

Our findings indicate that alemtuzumab-induced GD usually requires longer treatment with ATD. After a median follow-up time of 72 months, more than 40% of the patients still had active disease, and the time to TRAb seroconversion was 22 months for those who achieved remission. These results contrast with the course of conventional GD, where more than 70% achieve TRAb normalization within 12 to 18 months (15). However, there are conflicting observations regarding the remission rate and long-term outcomes for alemtuzumab-induced GD (1, 8, 9), and some studies report a greater number of GD patients needing definitive therapy (6, 16). We found that none of the patients relapsed, indicating an excellent long-term prognosis for alemtuzumab-induced GD if remission is obtained.

Our study found that more women than men treated with alemtuzumab developed GD, which is consistent with previous research (5, 17). Women are known to have a higher risk of developing autoimmune diseases in general, and the female to male ratio for GD is 5:1 (18). Younger age was the only identified risk factor for GD in our study. Notably, earlier MS treatment with interferon beta-1a and -1b, which is known to induce thyroid antibody production and autoimmune thyroid disease (19), did not increase the risk of developing GD after alemtuzumab treatment.

Development of GD after alemtuzumab treatment was associated with reduced risk of new MS attacks and lesions on MRI, consistent with earlier findings (20). The mechanism for this remains unclear but is interesting from an immunological standpoint. As only a few patients required further treatment after alemtuzumab, it is difficult to draw conclusions about the potential benefits of subsequent rituximab treatment.

The prevalence of TED is reported to be between 30% and 40% in conventional GD (21), but recent studies have observed a decreasing incidence (22, 23). Little information is available on TED in alemtuzumab-induced GD. Some studies have reported a lower incidence and milder cases of TED (24), but also severe cases have been described (25). We found that only 15% developed TED, and all cases were either mild or moderate. However, because of the small

Table 3. Treatment regimen, laboratory tests, and orbitopathy of the patients with Graves disease

Parameter	Study population ($n = 58$)
Treatment	
Antithyroid drugs	
Titration, *n* (%)	24 (41.4%)
Block and replace, *n* (%)	12 (20.7%)
Levothyroxine, *n* (%)	8 (13.8%)
Radioiodine, *n* (%)	2 (3.4%)
Thyroidectomy, *n* (%)	7 (12.1%)
Unknown or no treatment, *n* (%)	5 (8.6%)
Time (months) until termination of ATD treatment (months), median (range)	22 (2-58)
Laboratory	
TRAb positive, *n* (%)	58 (100%)
TPOab positive, *n* (%)	32 (55.2%)
TRAb Roche Cobas ($n = 47$) (U/L), median (range)	10.8 (3-300)
TRAb Phadia 2500 ($n = 8$) (U/L), median (range)	24 (5-69)
TPOab (kIU/L), median (range)	134 (36-939)
TSH (mU/L) at onset of thyroid disease, median (range)	0.01 (0-109)
Serum FT4 at onset of thyroid disease (pmol/L), median (range)	29.6 (2-100)
Serum FT3 at onset of thyroid disease (pmol/L), median (range)	11.5 (2-37)
Fluctuating thyroid hormone levels, *n* (%)	24 (41.4%)
TED	
Patients with TED, *n* (%)	9 (15.5%)
Duration of thyroid disease before TED (months), median (range)	17 (0-49)
Duration from alemtuzumab to TED (months), median (range)	40.5 (18-81)
CAS at diagnosis of TED, median (range)	1 (0-3)
Severity after EUGOGO criteria	
- Mild, *n* (%)	7 (77.8%)
- Moderate to severe, *n* (%)	2 (11.1%)
- Sight-threatening, *n* (%)	0 (0%)
Treatment of	
- Artificial eye drops, *n* (%)	6 (66.7%)
- Selenium, *n* (%)	1 (22.2%)
- Corticosteroids (intravenous), *n* (%)	2 (22.2%)

Reference levels: TSH 0.40-4.50 (mU/L), FT4 9.5-22.0 pmol/L, FT3 3.1-6.8 pmol/L, TPOab <34 kIU/L, TRAb Roche cobas <1.75 U/L, TRAb Phadia 2500 < 3.3 kIU/L.
Abbreviations: ATD, antithyroid drugs; CAS, Clinical Activity Score; EUGOGO, European Group on Graves' Orbitopathy; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves disease; TED, thyroid eye disease; TSH, thyroid-stimulating hormone; TPOab, thyroid peroxidase antibody; TRAb, thyrotropin receptor antibody.

sample size, we could not determine whether the severity of alemtuzumab-
induced TED differs from that observed in conventional GD.

Four patients with active GD successfully completed pregnancy without complications. Of note, 3 of the women had TRAb levels more than 3 times the upper reference limit, suggesting a potential risk to the fetus. Although only a few cases are reported here, these findings provide important clinical experience regarding pregnancy and outcome for MS patients receiving alemtuzumab treatment.

Several theories have been proposed to explain the pathogenesis of alemtuzumab-induced GD. Following treatment, T cells and B cells begin to repopulate lymphoid organs, but at different time points ranging from days to weeks. The prevailing hypothesis is that B-cell repopulation precedes that of T cells, leading to the production of TRAb without T-cell-mediated regulation to protect against autoimmunity (26, 27). Our data revealed a median period of 25 months from the first dose of alemtuzumab to thyroid dysfunction (Fig. 2), which is consistent with previous studies reporting a peak in GD incidence during the third year after start of treatment. This coincides with the peak levels of circulating B cells, which rises to 124% of baseline 27 months after alemtuzumab treatment (27). Interestingly, high doses of alemtuzumab are being used in the treatment of vasculitis, rheumatoid arteritis, and chronic lymphatic leukemia without inducing thyroid dysfunction. The reason for this discrepancy is unknown, but it could be related to differences in dose and duration of treatment as well as increased susceptibility to autoimmunity in MS patients compared to those with other conditions (27).

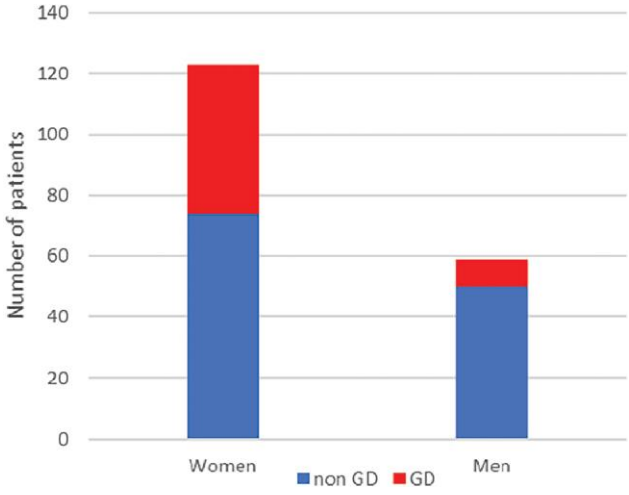

Figure 1. Number of alemtuzumab treated patients with and without development of Graves disease by gender.

One of the key strengths of this study is the unbiased recruitment of participants, since more than 90% of treated patients within a large geographical area were enrolled and completed the study. This represents a real-world experience from clinical practice with high external validity. A limitation is the retrospective collection of data, partly compensated for by follow-up data from medical records. Furthermore, the small numbers of smokers, patients with TED, and pregnancies preclude definite conclusions about these subgroups. In addition, there was no extended follow-up of the children born to mothers with GD beyond what was written in the medical records at birth. We also have to mention that, while for many years Norway has been considered an iodine-sufficient country, recent findings have confirmed inadequate iodine intake among subgroups, including pregnant and lactating women, vegans, and certain immigrant groups (28).

In conclusion, this study provides a comprehensive characterization of the course of alemtuzumab-induced GD, which occurs in 30% of patients. Our data clearly demonstrate that the time to remission is significantly longer than in conventional GD, and a large proportion of patients did not achieve remission at all. However, if remission was obtained, no relapses were observed. A much higher prevalence of fluctuating thyroid function was observed than previously reported. Younger patients and women were more prone to develop alemtuzumab-induced GD, but no other risk factors were identified. This study underscores the importance of systematic, long-term monitoring of thyroid function and the liberal use of block-and-replace treatment.

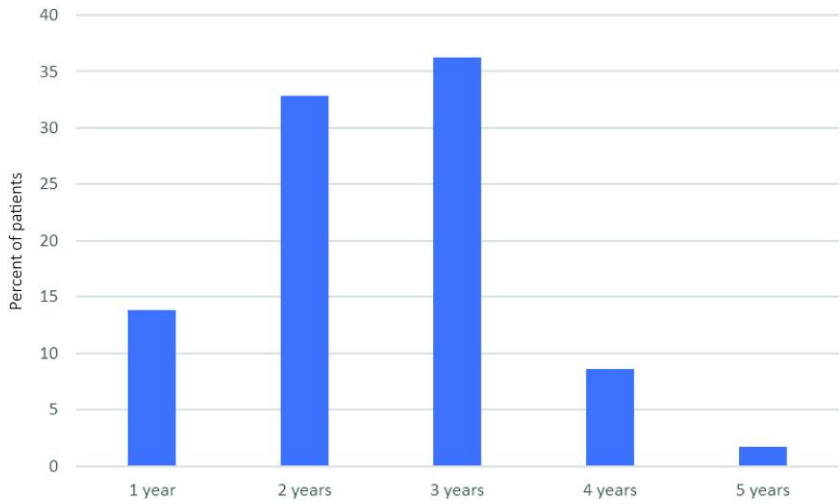

Figure 2. Percent of patients that developed Graves disease each year after alemtuzumab treatment (calculated as median time from first dose of alemtuzumab to diagnosis of Graves disease, divided by years).

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Disclosures

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

Data Availability

All original data generated and analyzed during this study are included in this published article.

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