Graves' disease with fluctuating thyroid status and hypothyroidism with positive anti-TSH receptor antibody levels: distinctive autoimmune side-effects following alemtuzumab therapy for MS

N Pariani[1], M Willis[2], I Muller[4], S Healy[2], T Nasser[2], J Jones[3], VKK Chatterjee[1], C Dayan[4], N Robertson[2], A Coles[3], C Moran[1]

Wellcome-MRC Institute of Metabolic Science[1] and Department of Clinical Neurosciences[3], University of Cambridge, Department of Neurology, University Hospital Wales, Cardiff[2] & Institute of Molecular & Experimental Medicine, Cardiff University[4]

UNIVERSITY OF CAMBRIDGE

INTRODUCTION

- Alemtuzumab is a humanised monoclonal Ab targeting CD52 antigen on T & B lymphocytes and it leads to rapid and sustained lymphocyte depletion.
- It is a very effective treatment for multiple sclerosis (MS) and it has been recently approved for relapsing-remitting MS treatment.
- Principal adverse effect of alemtuzumab is novel autoimmunity arising months to years after treatment:
  - ✓ most common target is the thyroid, being affected in 15-30% of alemtuzumab-treated MS patients;
  - ✓ Graves' disease (GD) accounts for 60-70% of thyroid autoimmunity;
  - ✓ published literature suggests that alemtuzumab-induced GD has a more indolent course, with good response to medical treatment.

AIM AND METHODS

Aim

To determine type, frequency and course of alemtuzumab-induced thyroid dysfunction (TD).

Methods

Case record review of MS patients who developed TD after alemtuzumab treatment in Cambridge and Cardiff.

Definitions

- Graves' disease: hyperthyroidism with positive anti-TRAb *and/or* increased tracer uptake on Technetium scan
- Hashimoto's thyroiditis (HT): positive anti-TPO Ab with a negative anti-TRAb titre and raised TSH
- Thyroiditis: thyrotoxicosis followed by spontaneous eu/hypothyroidism with negative anti-TRAb and anti-TPO *and/or* no tracer uptake on Technetium scan

RESULTS

Our cohort

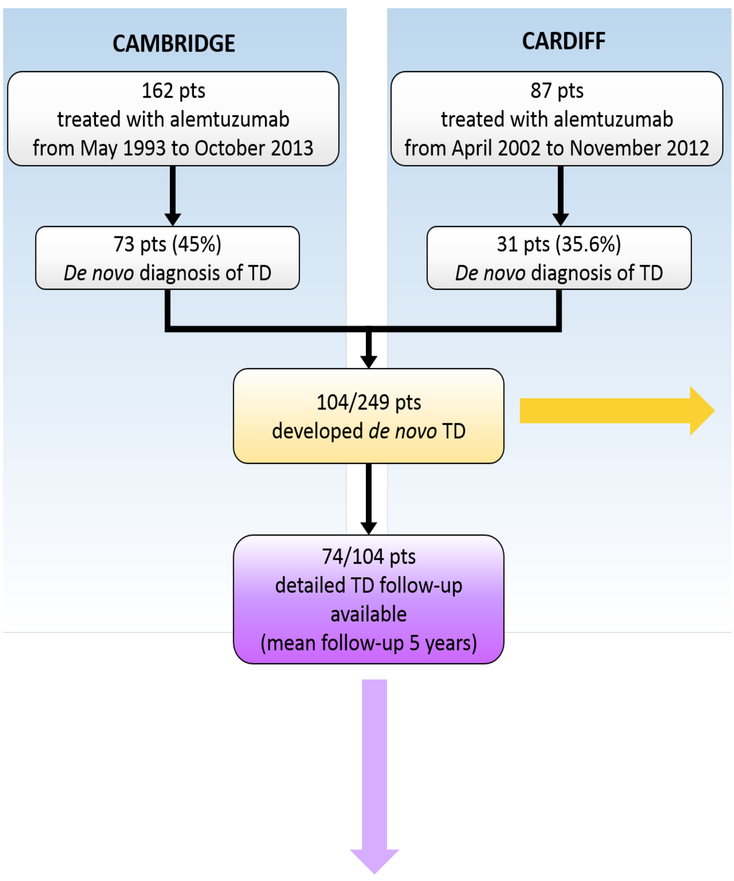


Table 1. Characteristics of all patients (n=104)

Gender	Age	Interval to TD onset after last dose alemtuzumab	Type of TD
Female 78% (n=81) Male 22% (n=23)	Mean 37.7 ± 9 years (range 20-60 years)	Mean 22.7 ± 18 months (range 2-107 months)	GD 69% (n=72) Hypo TRAb+ 11.5% (n=12) HT 7.7% (n=8) Thyroiditis 4.8% (n=5) Hypo seronegative 3% (n=3) Hyper unspecified 2% (n=2) Unknown 2% (n=2)

- 11 of 72 patients with GD had variable course switching from hypo to hyperthyroidism or vice versa (table 2).
- High proportion of patients (11.5%) with TRAb+ that experienced only hypothyroidism.
- GD was not particularly associated with extrathyroidal manifestations:
  - ✓ None had pretibial myxoedema or acropachy;
  - ✓ 7 of 62 patients TRAb+ (11.3%) had signs of ophthalmopathy.

Table 2. Details of subset of patients with fluctuating GD (n=11)

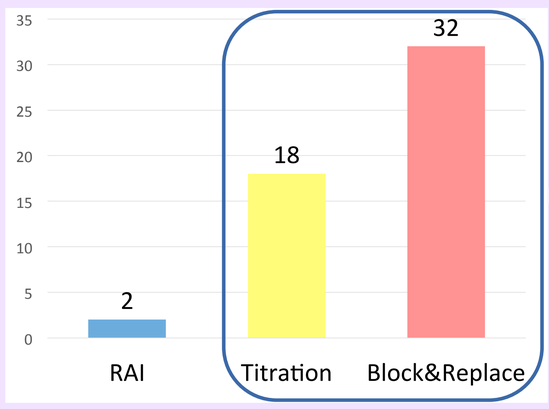
Patient No.	1° TD episode		2° TD episode		3° TD episode	
	Type	TRAb bioactivity	Type	TRAb bioactivity	Type	TRAb bioactivity
1	Hypo	TSAb + TBAb +/-	Hyper	TSAb ++ TBAb -	-	-
2	Hypo	TSAb +/- TBAb ++	Hyper	TSAb - TBAb +	-	-
3	Hyper	TSAb +/- TBAb -	Hypo	TSAb ++ TBAb ++	Hyper	TSAb + TBAb -
4	Hyper	TSAb - TBAb -	Hypo	TSAb - TBAb +/-	Hyper	TSAb ++ TBAb +/-
5	Hypo	TSAb ++ TBAb ++	Hyper	TSAb - TBAb +/-	-	-
6	Hyper	TSAb +/- TBAb +	Hypo	TSAb + TBAb ++	Hyper	TSAb - TBAb +/-
7	Hypo	N/A	Hyper	N/A	-	-
8	Hypo	N/A	Hyper	N/A	-	-
9	Hyper	N/A	Hypo	N/A	Hyper	N/A
10	Hypo	TSAb ++ TBAb ++	Hyper	TSAb ++ TBAb +	-	-
11	Hypo	TSAb +/- TBAb -	Hyper	N/A	-	-

TSAb = thyroid stimulating antibody
TBAb = thyroid blocking antibody

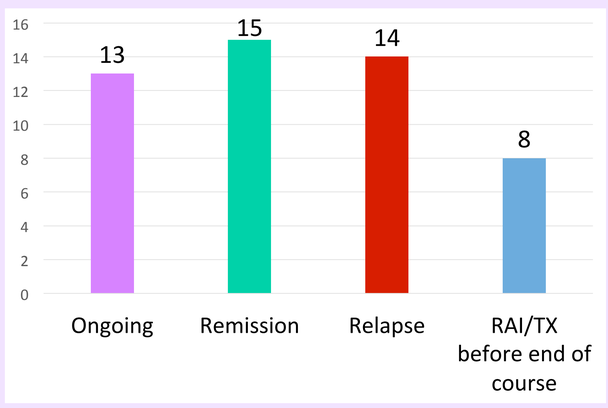
Table 3. Type of TD in patients with detailed follow-up (n=74)

Type of TD	N. patients
GD	70.3% (n=52)
Hypo TRAb+	13.5% (n=10)
HT	9.5% (n=7)
Thyroiditis	4.1% (n=3)
Hypo sieroneg	1.3% (n=1)
Hyper unspecified	1.3% (n=1)

Initial treatment hyper (n=52)



Response to medical therapy (n=50)



- Rate of relapse in patients that completed a course of medical treatment was similar to conventional GD (around 50%).
- 8 patients had definitive treatment before end of course of medical treatment mainly because of difficult control of TFTs on ATDs.

SUMMARY

- In our cohort, TD occurred more frequently than previously described (42%).
- GD was confirmed to be the most common cause of TD after alemtuzumab (69%).
- Relapse rate was not lower than in conventional GD and perhaps higher.
- Fluctuating and unpredictable course of GD and high frequency of TRAb+ hypothyroidism suggests switch of blocking to stimulating TRAb; we have been demonstrated the presence of both stimulating and blocking TRAb in these patients.

CONCLUSION

- Alemtuzumab is superior to conventional MS treatment and recently approved, so will be used more often.
- High frequency of fluctuating course of alemtuzumab-induced GD means close monitoring is required.
- Switching of blocking to stimulating Abs may be the explanation of fluctuating course of GD but further studies are required to confirm this hypothesis.

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Thyroid

Nadia Pariani

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