

Autoimmunity and long-term safety and efficacy of alemtuzumab for multiple sclerosis: Benefit/risk following review of trial and post-marketing data

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Abstract

Does pre-existing or treatment-emergent autoimmunity increase the risk of subsequent autoimmune disease in individuals with relapsing remitting multiple sclerosis (MS) after alemtuzumab? In the extended phase 2/3 trials, 34/96 (35.4%) patients with, and 395/1120 (35.3%) without, pre-existing autoimmunity developed non-MS autoimmunity. Thyroid autoimmunity after alemtuzumab courses 1 or 2 did not increase subsequent non-thyroid autoimmune adverse events. Therefore, autoimmune disease before or after alemtuzumab treatment does not predict autoimmunity after further courses, so should not preclude adequate alemtuzumab dosing to control MS. Finally, post-marketing safety data contribute towards a full record of the alemtuzumab benefit/risk profile for the MS field.

Clinical trial information:

CAMMS223 [NCT00050778]; <https://clinicaltrials.gov/ct2/show/NCT00050778>

CARE-MS I [NCT00530348]; <https://clinicaltrials.gov/ct2/show/NCT00530348>

CARE-MS II [NCT00548405]; <https://clinicaltrials.gov/ct2/show/NCT00548405>

CARE-MS extension [NCT00930553];

<https://www.clinicaltrials.gov/ct2/show/NCT00930553>

TOPAZ [NCT02255656]; <https://clinicaltrials.gov/ct2/show/NCT02255656>

Introduction

In 2019, the European Medicines Agency altered the license of alemtuzumab, a high-efficacy drug for MS, to contraindicate use in patients with “concomitant autoimmune diseases (besides MS),” which we interpret as pre-existing autoimmunity or autoimmunity emerging after alemtuzumab.¹ This change was designed to reduce risk of rare, serious events, such as immune thrombocytopenia or autoimmune renal or liver disease. Other rare but serious side effects were also considered, including peri-infusion cardiovascular adverse events (AEs).¹

We report data from clinical trials on risk of subsequent autoimmune AEs in alemtuzumab-treated patients with pre-existing or treatment-emergent autoimmunity. We additionally report safety events encountered post-marketing to contribute towards a complete overview of risks of alemtuzumab.

Methods

Designs of the CAMMS223 (NCT00050778) and CARE-MS studies (NCT00530348, NCT00548405) and extensions (NCT00930553 and NCT02255656) were described previously.²⁻⁶ Exclusion criteria included antithyroid stimulating hormone receptor antibodies or clinically significant autoimmunity including immune cytopenias, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease, and severe psoriasis.

Clinical trial data were assessed for impact of pre-existing non-MS autoimmunity on risk of developing autoimmunity after alemtuzumab. We also assessed whether emergence of the commonest autoimmune disease after alemtuzumab, thyroid disease, after courses 1 and 2 was associated with development of autoimmune

nephropathy, immune thrombocytopenia, acquired hemophilia or antiglomerular basement membrane disease following subsequent treatment courses. Statistics were performed via chi-square tests. Rates of malignancies, serious infections, *Listeria* infections, herpetic infections, and deaths were also reported.

Novel AEs reported post-marketing were assessed from the manufacturer's pharmacovigilance database and divided into peri-infusion (during or within 7 days post-infusion) or delayed events (peak incidence 18–36 months post-treatment).

Autoimmune AE monitoring was conducted per protocol in clinical trials^{2,4,5} and per labeling and the Risk Evaluation and Mitigation Strategy/Risk Management Plan post-marketing.⁷ The risk of delayed autoimmune events was defined as peak incidence occurring 18–36 months post-treatment.

Results

Clinical trial efficacy and patient retention

Efficacy of alemtuzumab versus subcutaneous interferon beta-1a was established in the core clinical studies^{2,4,5} and was maintained long-term. Over 9 years in pooled CARE-MS I and II alemtuzumab patients, 64% remained free of 6-month confirmed disability worsening, 45% achieved 6-month confirmed disability improvement, mean Expanded Disability Status Scale score change was +0.21, and cumulative median brain volume change was –1.65%.⁶ Patient retention rates were 75% (CARE-MS I) and 66% (CARE-MS II) through Year 9.⁶

Clinical trial safety outcomes

Autoimmune AEs after alemtuzumab were similar between patients with pre-existing non-MS autoimmunity (34/96 patients [35.4%]) and those without (395/1120 [35.3%]; Table 1). Pre-existing autoimmunity did not predict additional autoimmunity (Table

1). In patients with or without pre-existing autoimmunity, post-alemtuzumab autoimmune AEs were serious in 8.8% (3/34) and 9.1% (36/395) of cases, respectively. In CAMMS223, 66.7% of the 9/119 patients with baseline antithyroperoxidase (anti-TPO) antibodies developed autoimmunity after alemtuzumab versus 26.4% of 110/119 patients without these antibodies ($p=0.0107$). Of CARE-MS patients with high (>34 IU/mL, $n=80/1084$) or normal ($1-34$ IU/mL, $n=1004/1084$) baseline anti-TPO antibody levels, 51.3% and 34.6% developed post-baseline autoimmunity, respectively ($p=0.0027$).

Autoimmune AE incidence after course 2 was similar and low in patients with or without thyroid AEs between courses 1 and 2 (0/53 [0%] vs 25/841 [3.0%]; Figure 1). Likewise, autoimmune AE rates after course 3 were similar and low between patients with and without thyroid AEs between courses 2 and 3 (2/110 [1.8%] vs 6/301 [2.0%]).

In patients treated with alemtuzumab 12 mg ($N=1216$; 9021 patient-years' follow-up), 26 (2.1%) experienced malignancies; this unadjusted incidence rate is not higher than the age-adjusted rate in the overall US population (2.88 vs 4.42 per 1000 person-years, respectively).⁸ Serious post-alemtuzumab infections occurred in 113 patients (9.3%). *Listeria* meningitis (grade 2) occurred in one patient, 12 days after completing course 1 of alemtuzumab 24 mg. Herpetic infections occurred in 330 patients (27.1%), most commonly herpes zoster ($n=173$ [14.2%]) and oral herpes ($n=130$ [10.7%]). Nine (0.74%) and two (0.16%) patients experienced myocardial infarctions or stroke (ischemic stroke and cerebral hemorrhage), respectively, occurring ≥ 136 days post-infusion. Over 9 years, 19 (1.6%) deaths (2.1 per 1000 patient-years) were reported in patients exposed to alemtuzumab 12 mg (overall age-adjusted US death rate: 7.3 per 1000 person-years).⁹

Post-marketing safety

As of March 31, 2019, post-marketing data included 25,292 patients with alemtuzumab exposure.

Peri-infusion AEs reported post-marketing included hemorrhagic stroke (2.8 in 10,000 patients), pulmonary alveolar hemorrhage (4.3 in 10,000 [unrelated to antiglomerular basement membrane disease]), other stroke (0.8 in 10,000), myocardial infarction (2.0 in 10,000), and cervicocephalic arterial dissection (1.6 in 10,000). Among 21 cases of symptoms/signs consistent with acute coronary syndrome within 72 hours post-infusion, none were fatal, three had acute myocardial infarction, and nine were in ≤ 40 -year-old patients. A majority (15/21) had risk factors for cardiovascular disease. Of the 13 patients with hemorrhagic or ischemic stroke, seven reported 'blood pressure increase' during infusion. Ischemic strokes were associated with cervicocephalic arterial dissection. One hemorrhagic stroke was fatal.

The reported post-marketing cases of delayed autoimmune hepatitis (10.7 in 10,000) had 12–29-month onset time. No autoimmune hepatitis cases occurred >4 years after dosing. Reported hemophagocytic lymphohistiocytosis cases (2.7 in 10,000) occurred a few months to 4 years following treatment initiation, with two associated deaths.

Listeriosis was reported in 77 patients post-marketing (30.4 in 10,000).

Discussion

In this analysis of clinical trials, pre-existing autoimmunity did not predict autoimmunity emerging after alemtuzumab. This conclusion is based on 96 patients with baseline autoimmunity, because serious autoimmune disease was an exclusion

criterion. Likewise, from the larger cohort without pre-existing autoimmunity (N=1120), emergence of thyroid autoimmunity after the first or second course, usually in the third year following treatment,²⁻⁶ did not increase the risk of further autoimmunity after subsequent courses. Importantly, we did observe significantly higher risk of post-alemtuzumab autoimmunity in patients with positive or higher than normal anti-TPO antibodies. Post-marketing data confirmed low absolute risk for peri-infusion, non-autoimmune AEs, including cardiovascular and pulmonary events, consistent with product labeling.

In our opinion, these findings, coupled with knowledge that thyroid disorders with alemtuzumab are rarely serious,¹⁰ suggest thyroid autoimmunity should not preclude further alemtuzumab treatment. Instead, this contraindication leaves patients—who would otherwise be appropriate candidates—incompletely treated and denied the full benefit of alemtuzumab.

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Declaration of conflicting interests

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Research ethics and patient consent

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Patients enrolled in the CAMMS223, CARE-MS I, CARE-MS II, CAMMS03409, and TOPAZ studies provided written informed consent, and all procedures were approved by local institutional ethics review boards of participating sites.

Previous presentation of data

Some of the data included in this manuscript were presented at the 6th Congress of the European Academy of Neurology, May 23-26, 2020 (Virtual Congress), and the Virtual Joint ACTRIMS-ECTRIMS 2020 Meeting, September 11-13 (MSVirtual2020).

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Table 1. Effect of pre-existing non-MS autoimmunity on the development of additional autoimmunities in clinical trials.

Pre-existing autoimmunity	N	No post-baseline autoimmune AE n (%)	Exactly 1 post-baseline autoimmune AE n (%)	≥2 post-baseline autoimmune AE n (%)
Patients with no pre-existing autoimmunity	1120	725 (64.7)	303 (27.1)	92 (8.2)
Patients with pre-existing autoimmunity	96	62 (64.6)	29 (30.2)	5 (5.2)
Hypothyroidism	37	26 (70.3)	10 (27.0)	1 (2.7)
Hyperthyroidism	7	4 (57.1)	3 (42.9)	0
Autoimmune thyroiditis	6	4 (66.7)	0	2 (33.3)
Eczema	19	7 (36.8)	12 (63.2)	0
Psoriasis	19	15 (79.0)	4 (21.1)	0
Alopecia	14	9 (64.3)	4 (28.6)	1 (7.1)
Crohn's disease	1	0	0	1 (100)
Guillain-Barré syndrome	1	1 (100)	0	0

Pooled CAMMS223, CARE-MS I, and CARE-MS II trials for patients treated with alemtuzumab 12 mg/day or patients treated with SC IFNB-1a in the core studies who switched to alemtuzumab 12 mg/day in the extension studies. Pre-existing autoimmune events included the following: hypothyroidism, hyperthyroidism, autoimmune thyroiditis, psoriasis, eczema, alopecia, antiphospholipid syndrome, Crohn's disease, and Guillain-Barré syndrome. Post-baseline autoimmune events included the following: hypothyroidism, hyperthyroidism, autoimmune thyroiditis, psoriasis, eczema, alopecia, antiphospholipid syndrome, Crohn's disease, Guillain-Barré syndrome, acquired hemophilia, antglomerular basement membrane antibody positive, nephropathy, and immune thrombocytopenia. Serious post-baseline

autoimmune AEs occurred in one patient with pre-existing hypothyroidism, one patient with pre-existing psoriasis, and one patient with pre-existing Crohn's disease. An event was considered at post-baseline if it occurred after the first alemtuzumab dose up to 9 years (for patients treated with alemtuzumab 12 mg/day), and if it occurred within 7 years from first alemtuzumab dose (for patients treated with SC IFNB-1a in the core studies and who switched to alemtuzumab 12 mg/day in the extension studies).

AE: adverse event; MS: multiple sclerosis; SC IFNB-1a: subcutaneous interferon beta-1a.

Figure 1. Effect of post-alemtuzumab thyroid AEs on subsequent development of immune thrombocytopenia, acquired hemophilia, antiglomerular basement membrane antibody positive, or nephropathy in clinical trials.

Pooled CAMMS223, CARE-MS I, and CARE-MS II trials for patients treated with alemtuzumab 12 mg/day. Treatment-emergent thyroid AEs include the following: antithyroid antibody positive, autoimmune thyroiditis, Basedow's disease, blood thyroid stimulating hormone abnormal, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, endocrine ophthalmopathy, exophthalmos, goiter, hyperthyroidism, hypothyroidic goiter, hypothyroidism, myxoedema, primary hypothyroidism, thyroid cyst, thyroid dermatopathy, thyroid disorder, thyroid function test abnormal, thyroid mass, thyroid pain, thyroidectomy, thyroiditis, thyroiditis subacute, thyrotoxicosis, thyroxine binding globulin increased, thyroxine decreased, thyroxine free decreased, thyroxine free increased, thyroxine increased, toxic nodular goiter, triiodothyronine decreased, triiodothyronine free decreased, triiodothyronine free increased, triiodothyronine increased, and triiodothyronine uptake decreased. Subsequent autoimmune events include any nephropathy event, any immune thrombocytopenia event, acquired hemophilia, and antiglomerular basement membrane antibody positive.

AE: adverse event; MS: multiple sclerosis.

