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ORIGINAL ARTICLE

Alemtuzumab-induced thyroid events in multiple sclerosis: a systematic review and meta-analysis

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Abstract

Purpose Autoimmune thyroid events (ATEs) are common side effects after alemtuzumab (ALZ) therapy in patients with multiple sclerosis (MS). Our purpose was to reach more robust evidence on prevalence and outcome of the spectrum of alemtuzumab-induced autoimmune thyroid events in patients with multiple sclerosis.

Methods PubMed and Scopus were systematically searched through July 2019. Studies dealing with patients without personal history of thyroid dysfunctions and affected by MS treated with ALZ and reporting ATEs were selected. Data on prevalence and outcome of ATEs were extracted. A proportion of meta-analysis with random-effects model was performed.

Results Considering the overall pooled number of 1362 MS patients treated with ALZ (seven included studies), a 33% prevalence of newly diagnosed ATEs was recorded. Among all ATEs, Graves' disease (GD) was the most represented [63% of cases, 95% confidence interval (CI) 52–74%], followed by Hashimoto thyroiditis (15%, 95% CI 10–22%). Interestingly, GD showed a fluctuating course in 15% of cases (95% CI 8–25%). Of all GD, 12% (95% CI 2–42%) likely had spontaneous remission, 56% (95% CI 34–76%) required only antithyroid drugs, 22% (95% CI 13–32%) needed additional RAI, and 11% (95% CI 0.9–29%) underwent definitive surgery.

Conclusion Among different categories of ATEs, Graves' hyperthyroidism was the most common thyroid dysfunction, occurring in more than half of cases. Antithyroid drugs should represent the first-line treatment for ALZ-induced GD patients. However, alemtuzumab-induced GD could not be considered as having a more favourable outcome than conventional GD, given the substantial chance to encounter a fluctuating and unpredictable course.

Keywords Multiple sclerosis · Alemtuzumab · Thyroid · Side effects

Abbreviations

ALZ	Alemtuzumab
AAEs	Adverse autoimmune events
MS	Multiple sclerosis
ATE(s)	Autoimmune thyroid event(s)
GD	Graves' disease
GREAT	Graves' recurrent events after therapy
CSS	Clinical severity score
CLL	Chronic lymphocytic leukemia
RCTs	Randomized controlled trials
TPOAb	Thyroid peroxidase antibody
TRAb	Thyrotropin receptor antibodies
HT	Hashimoto thyroiditis
ST	Silent thyroiditis
GO	Graves' orbitopathy
ATD	Antithyroid drugs
RAI	Radioiodine

Introduction

Alemtuzumab (ALZ), a humanised monoclonal antibody, targets $CD52^+$ cells determining their depletion followed by repopulation [1]. Lymphocytes escaped from cytolysis undergo homeostatic proliferation, potentially setting up an exaggerated and self-oriented response behind adverse autoimmune events (AAEs) [2]. AAEs are the most important and common side effects due to ALZ in patients with multiple sclerosis (MS) and they chiefly affect thyroid gland [2].

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Indeed, thyroid dysfunction in alemtuzumab-treated MS patients is a common issue in clinical practice. The overall prevalence of autoimmune thyroid events (ATEs) after ALZ use seems to range from 34 to 41.1%, with Graves' disease (GD) appearing to be the leading thyroid event [3, 4]. It has been proposed that ALZ-induced GD shows a more favourable course and a higher rate of remission with antithyroid drugs than conventional GD [5, 6]. Nevertheless, a growing body of evidence would suggest that ALZ-induced ATEs can present complex and unique features, namely: GD may exhibit a fluctuating and unpredictable course [3, 4]; a single individual may experience more than one ATEs [3, 4]; a greater number of GD cases need a definitive therapy [i.e., radioiodine (RAI) or surgery] [4, 7].

Therefore, the present study was undertaken to achieve more robust evidence on the association between alemtuzumab and autoimmune thyroid disease in patients with MS. In particular, here, we systematically reviewed the literature on this topic and undertook a meta-analysis of available data aiming to establish the precise prevalence and the peculiar features of the different categories of ATEs. Yet, we aimed to estimate both the outcome and severity of alemtuzumab-induced GD.

Methods

In this systematic review and meta-analysis, all procedures adopted were consistent with PRISMA guidelines [8]. This study did not require ethical approval, because there was no human or animal experiment.

Search strategy

Two investigators (L.S. and P.T.) independently conducted a comprehensive literature on the online databases of MEDLINE (PubMed) and Scopus using the following search terms and their combinations: "Alemtuzumab" (or "Campath-1H"), "side effects" (or "thyroid"). A beginning date limit was not used and the final search was carried on 21 July 2019, considering studies in any language. The search strategy was refined to evaluate all references of the screened articles to potentially identify additional studies.

Study selection

Records identified by our search strategy were screened employing as the major selection criterion "the use of ALZ in patients with multiple sclerosis", therefore excluding the studies dealing with ALZ as medication for other diseases [i.e., chronic lymphocytic leukemia (CLL), rheumatoid arthritis, Behçet's disease, allogeneic hematopoietic stem cell transplantation, and islet and kidney transplantation]. In addition, only original papers reporting the issue of "thyroid event/dysfunction associated with ALZ use" were considered for inclusion [they could be randomized controlled trials (RCTs), observational studies, and case series]. Excluded were following: (a) case reports, reviews, editorials, letters, commentaries, and meeting abstracts; (b) precursor RCTs with shorter follow-up than RCTs included in the meta-analysis; (c) small case series (less than ten patients); (d) original papers not having accurate data (clinical and/or laboratory) about categories of ATEs neither details about GD outcome/management; (e) original papers where the patients had thyroid dysfunctions before alemtuzumab therapy; (f) studies with overlapping data. Two researchers (L.S. and P.T.) independently reviewed titles and abstracts of the screened articles, applying the above criteria. Then, all authors autonomously reviewed the full text of the eligible articles to determine their inclusion. Disagreements were resolved in collegial meetings.

Data extraction

For the included studies, the following data were coded and extracted independently and in duplicate by two investigators (L.S. and P.T.) in a piloted form: (a) author, publication year, study design; (b) number of patients treated with ALZ ("cohort", stating their gender, mean age, smoking habits) and the follow-up duration (months) after the first infusion of ALZ; (c) antibody profile prior and post-ALZ therapy [patients with positivity for thyroid peroxidase antibody (TPOAb) and/or for thyrotropin receptor antibodies (TRAb)]; (d) number of patients with ATEs in the cohort group and their age at diagnosis ["cases", divided into five categories or types of ATEs: GD, fluctuating GD, Hashimoto thyroiditis (HT), silent thyroiditis (ST), TRAb-positive hypothyroidism]; (e) number of cases with multiple ATEs (more than one episode or type of ATE); (f) timing of appearance of the first ATE (mean months or peak) from the most recent (last) infusion of ALZ; (g) influence of cumulative doses, intervals, and frequency of ALZ therapy on the genesis of ATEs; (h) severity of ATEs (overt or subclinical hypo- and hyperthyroidism); (i) number of patients with GD who also developed ocular manifestations [Graves' orbitopathy (GO)]; (l) outcome of cases with GD [number of patients who remitted spontaneously (spontaneous euthyroidism or hypothyroidism), who were treated with antithyroid drugs (ATD) alone or required definitive treatment (RAI or surgery)]. Where available, for the included papers, supplemental data sets (e-tables) were consulted to collect more detailed thyroid data. To code and extract the information about the above categories of ATEs, we adopted the following definitions:

- GD: low TSH with or without elevated FT4 or FT3 and positive TRAb;
- HT: raised TSH and positive TPOAb;
- ST: thyrotoxicosis followed by spontaneous euthyroidism or hypothyroidism, with negative TRAb;
- Fluctuating GD: unexpected fluctuations from hyperthyroidism to hypothyroidism (or vice versa), which could not be explained by omission or changes in therapy;
- TRAb-positive hypothyroidism: raised TSH with positive TRAb (with or without positive anti-TPO antibody).

To assess the severity of hyperthyroidism: (a) data according to international scores [9] were searched and extracted; (b) the recommended biochemical criteria [10] were used to distinguish overt hyperthyroidism from subclinical one; (c) other criteria (i.e., the need of therapy) to describe severity of Graves' hyperthyroidism were collected. Yet, spontaneous remission of GD occurred when, without any therapy, thyroid hormones spontaneously normalized or hypothyroidism developed. The collected data were cross-checked and any discrepancies were fully reconciled by joint re-evaluations.

Study quality assessment

The risk of bias of included non-RCTs was assessed independently by two reviewers (L.S. and M.Ca.) through National Heart, Lung, and Blood Institute Quality Assessment Tool. The risk of bias of included RCTs was assessed independently by the same reviewers through the Cochrane collaboration's tool for evaluating risk of bias for the following items: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selecting reporting. For other bias, funding was assessed.

Statistical analysis

The primary endpoint was the prevalence of GD and its fluctuating phenotype, HT, ST, and TRAb-positive hypothyroidism among patients developing autoimmune thyroid events after alemtuzumab therapy for MS. Secondary endpoints included: (a) assessment of autoimmune thyroid profile (TPOAb and TRAb positivity) of cohort and cases; (b) prevalence of single versus multiple ATEs among patients with ATEs; (c) severity and outcome of GD. Endpoints were assessed on a patient basis for each study. For statistically pooling data, a proportion meta-analysis was performed with DerSimonian and Laird method (random-effects model) [11]; in this model, pooled data are weighted averages relative to the sample size of the single studies. Pooled data were presented with 95% confidence intervals (95% CI) and displayed in a forest plot. I-square index was used to quantify the heterogeneity among the studies as follows: < 25%, no heterogeneity; 25–50%, mild heterogeneity; 50–75%, moderate heterogeneity; > 75%, high heterogeneity. Egger's test was carried out to evaluate the publication bias. Statistical analyses were performed using the StatsDirect statistical software (StatsDirect Ltd; Altrincham, UK). Both mean age of patients at development of first ATE and peak months of appearance of ATE from last ALZ use were expressed as means of determinations.

Results

Eligible articles

The literature search using the above algorithm and selection criteria yielded 1015 papers. All these records were screened in two main steps, and then, the full text of 25 potentially eligible articles was carefully considered. Of these 25 studies, 15 original articles (mono- or multicentric studies) did not have accurate thyroid data, as they only reported overall prevalence of thyroid dysfunction/disorder (without analyzing the various categories of ATEs) or they included patients with thyroid dysfunctions before alemtuzumab therapy. Other two studies (by Pariani et al. [4] and by Muller et al. [12]) were excluded as they contained overlapping data with the included studies. Similarly, as one of the co-authors of both the works told us, the paper by Tuohy et al. [13] was removed from meta-analysis as containing the same data sets of the article by Cossburn et al. [14]. E-tables by Cossburn et al. [14], Havrdova et al. [15], and Coles et al. [16] were consulted. After e-mailing with one of the co-authors of the latter three articles [14–16], we knew that in these papers, the conventional tools (i.e., thyroid hormones, TRAb, TPOAb, and thyroid scintigraphy) were used to make the final diagnosis of the specific type of thyroid adverse event. Thus, seven papers provided sufficient qualitative and quantitative data for systematic review and meta-analysis. Flowchart of study selection strategy is depicted in Fig. 1.

Qualitative analysis (systematic review)

The included studies were published between 1999 and 2017 by authors from UK, Czech Republic, USA, Germany. Among the seven included articles, there were four RCTs [3, 15–17], two prospective observational studies [14, 18], and one case series [7]. The overall number of patients affected by MS and treated with ALZ was 1362, and their mean age was comprised between 32 and 39 years, with female-to-male ratio ~ 2:1. The total number of patients of the cohort developing ATEs was 487, of which 380 could be categorized under each type of ATE. Autoimmune profile was assessed in a few studies: TPOAb positivity before ALZ

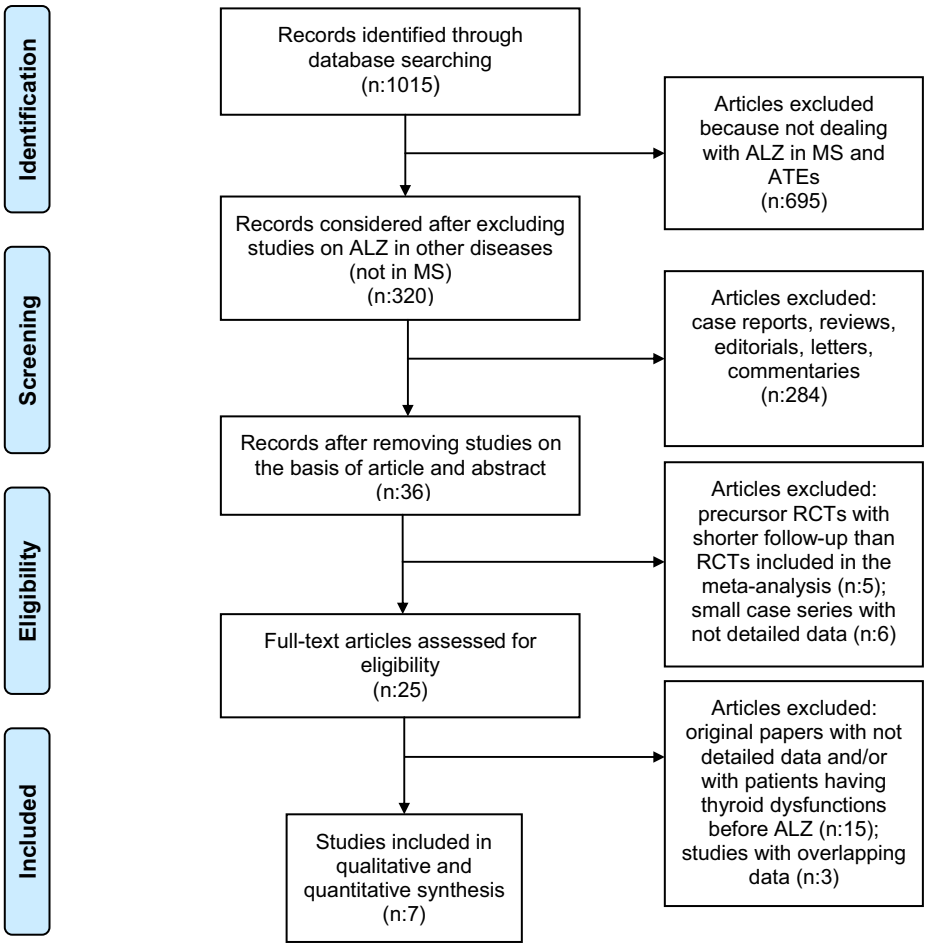

Fig. 1 Flowchart of study selection process

ALZ, alemtuzumab; MS, multiple sclerosis; RCTs, randomized controlled trials; ATEs, autoimmune thyroid events

was obtained from two studies [3, 14] and after ALZ just in one of them [3]; whereas TRAb dosage prior ALZ was carried out only in one study [17] and post-ALZ in two of them [3, 17]. There were only two studies reporting details about multiple ATEs in single individuals [3, 17] and three studies providing information as regards fluctuating GD cases [3, 7, 17]. Data concerning GO were available in four studies [3, 7, 16, 17]. Moreover, both severity and outcome aspects of ALZ-induced GD and specified therapy adopted (ATD alone or followed by definitive treatment) were stated in four studies [3, 7, 14, 17]. In any of the latter four studies, neither the Graves' recurrent events after therapy (GREAT) nor the clinical severity score (CSS) tools [9] were adopted to quantify the severity of GD. Yet, only two of them [3, 7] distinguished overt hyperthyroidism from subclinical form according to the definitions given in the guidelines [10], so that the meta-analytic result could not be calculated; since all four studies [3, 7, 14, 17] reported details of Graves's disease severity in terms of need therapy, the pooled result was still obtained. The median studies follow-up after first infusion of ALZ was 57 months ranging from 24 to 60 months. The time (mean months) of appearance of the first ATE from the most recent infusion of ALZ was recorded in six studies [3, 7, 14–17]. Finally, data concerning the influence of dose and/or interval and/or frequency of ALZ regimens on ATEs development were derived from three articles [3, 14, 17]. Table 1 summarizes the main characteristics of the seven included studies, while Supplemental Table 1 reports the overall characteristics of them. Table 2 gives the overview of the studies inclusion for the different endpoints.

Quantitative analysis (meta-analysis)

Table 3 details all pooled results of the current study. Considering 1362 MS patients treated with ALZ without previous history of thyroid dysfunctions, a 33% prevalence of newly diagnosed ATEs was recorded (Fig. 2). Mean age at first presentation of ATE was 35 years old, and the peak of ATEs from the last ALZ course was registered in month 28.5 with a very wide range (0.2–84 months). Gender assessment

Table 1 Summary of main characteristics of the seven articles included in the meta-analysis

First author (reference)	Year	Country	Median follow-up (months)	Cohort (*n*)	Cases (*n*)
Daniels [3]	2014	USA	57.3	216	73
Tsourdi [7]	2015	Germany	60	15	5
Cossburn [14]	2011	UK	34.3	248	41
Havrdova [15]	2017	Czech Republic	60	376	171
Coles [16]	2017	UK	60	435	174
Coles [17]	1999	UK	NR	27	9
Fox [18]	2012	USA	24	45	14
Total, *n*				1362	487

Median follow-up after first infusion of alemtuzumab; cohort = number of patients treated with ALZ; cases = number of patients developing ATEs among the cohort group

Table 2 Studies inclusion for the different endpoints

First author (reference)	ATEs categories	Mean age at ATE diagnosis	Mean months from the last ALZ	Influence of technical characteristics of ALZ therapy on ATEs	GD severity	Fluctuating GD	GO	GD outcome
Daniels [3]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tsourdi [7]	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Cossburn [14]	Yes	No	Yes	Yes	Yes	No	No	Yes
Havrdova [15]	Yes	No	Yes	No	No	No	No	No
Coles [16]	Yes	No	Yes	No	No	No	Yes	No
Coles [17]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Fox [18]	Yes	No	No	No	Yes	No	No	No

Yes/No indicates the inclusion of each study for the specific endpoint

ATEs autoimmune thyroid events, *GD* Graves' disease, *GO* Graves' orbitopathy

Table 3 Results of the meta-analysis on the overall series of articles and in specific subgroups

Outcome	Studies included (*n*)	MS patients (*n*)	Pooled prevalence (95% CI)	Heterogeneity (%)	Publication bias (*p*)
Patients with ALZ-induced ATEs*	7	1362	33 (24–43)	91.1	0.998
Type of ATE					
Graves'*	6	482	63 (52–74)	79.9	0.092
Overt	4	91	85 (70–95)	63.8	0.313
Subclinical	4	91	15 (5–30)	63.8	0.313
Fluctuating	3	62	15 (8–25)	0	NA**
With GO	4	144	11 (0.8–31)	83.9	0.012
In spontaneous remission	4	91	12 (2–42)	88.8	0.456
Treated with ATD only	5	113	56 (34–76)	79.4	0.565
Treated with RAI	5	113	22 (13–32)	27.8	0.775
Treated with surgery	4	91	11 (0.9–29)	75.5	0.121
Hashimoto thyroiditis*	6	482	15 (10–22)	59.7	0.476
Silent thyroiditis	5	468	9 (7–12)	0	0.859
Hypothyroidism with TRAb+	3	87	2 (0.1–6)	0	NA**

ATE autoimmune thyroid event, *ALZ* alemtuzumab, *GO* Graves' orbitopathy, *ATD* antithyroid drugs, *RAI* radioiodine, *TRAb+* positive thyrotropin receptor antibodies (with or without TPOAb, see also the text)

*Results reported in figures as forest plot; **Egger not calculable due to too few strata. Heterogeneity and publication bias were defined in the "Methods" section

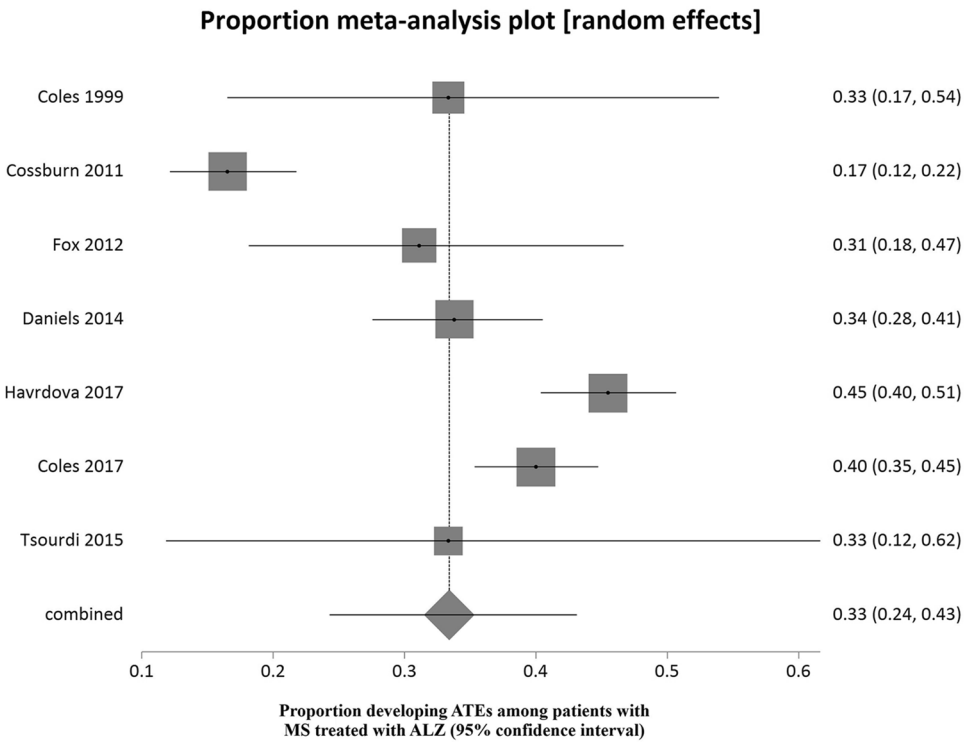

Fig. 2 Forest plot of pooled prevalence of patients developing ATEs among patients with MS treated with ALZ

among patients with ATEs could not be carried out because of unavailable data. Technical characteristics of ALZ therapy (i.e., the cumulative dose, the interval or the frequency) likely did not influence the development of ATEs. Among all ATEs, Graves' disease was the most represented occurring in 63% of cases (Fig. 3), followed by Hashimoto thyroiditis (15%) (Fig. 4), by silent thyroiditis (9%) and hypothyroidism with TRAb+ (2%). Graves' disease manifested as clinically overt type in 85% of patients, and it showed a fluctuating course in 15% of cases. Moreover, 11% of cases of GD

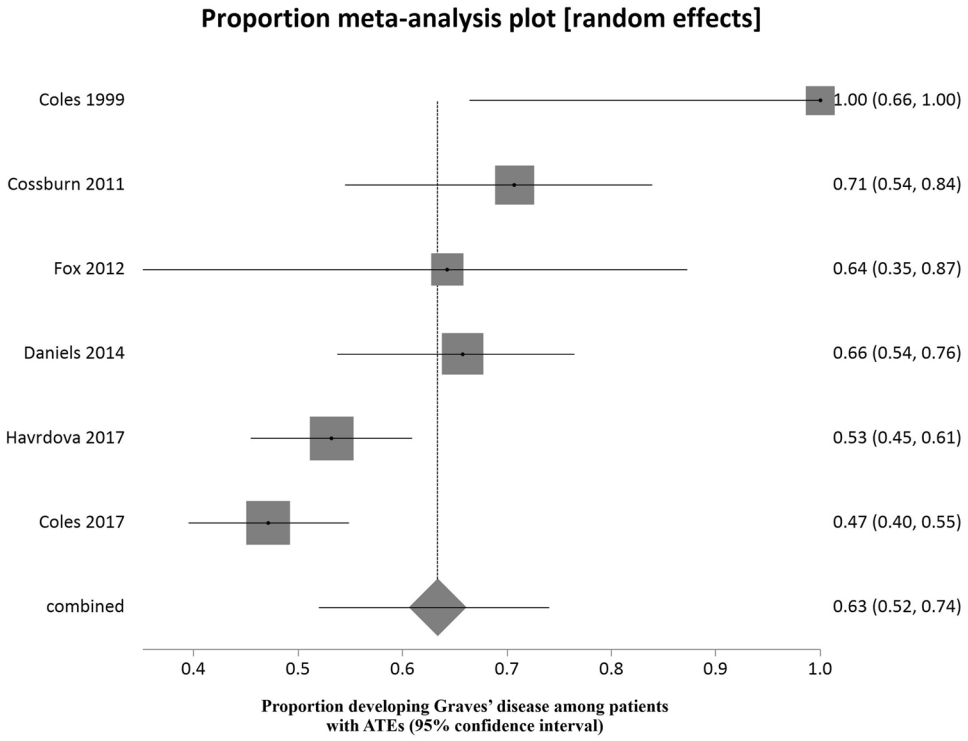

Fig. 3 Forest plot of pooled prevalence of patients developing Graves' disease among patients with ATEs

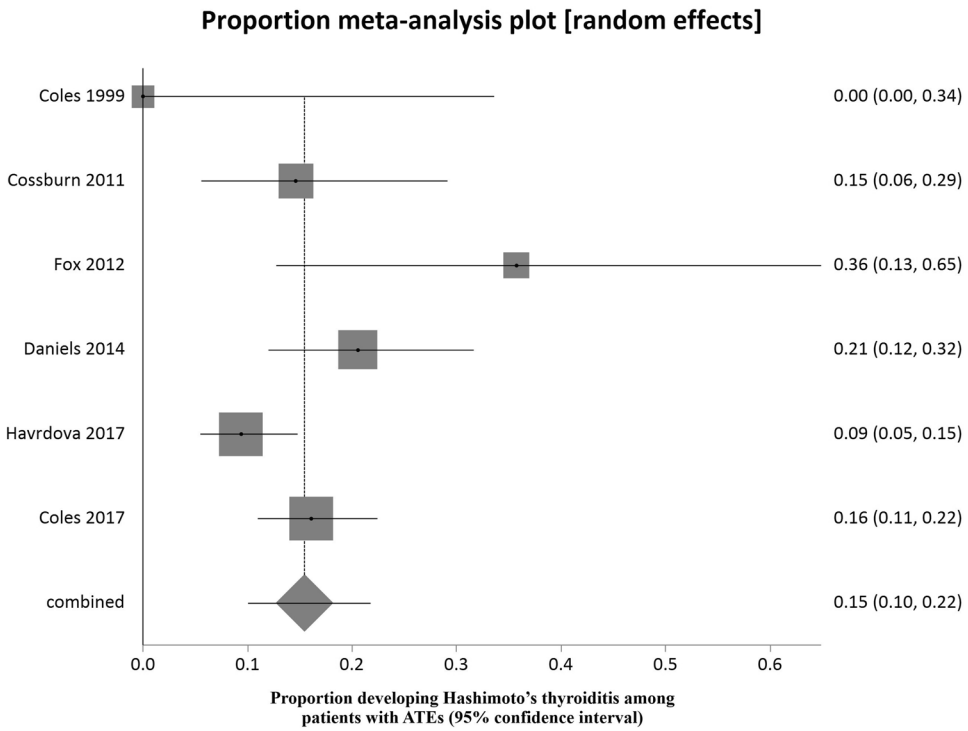

Fig. 4 Forest plot of pooled prevalence of patients developing Hashimoto's thyroiditis among patients with ATEs

were combined with orbitopathy. Of all Graves' patients, 12% remitted spontaneously, 56% required only antithyroid drugs, 22% needed additional RAI, and 11% underwent definitive surgery. Mild-to-high inconsistency was found in all the outcomes except for fluctuating Graves (absence of heterogeneity), prevalence of silent thyroiditis (absence of heterogeneity), and hypothyroidism with TRAb+ (absence of heterogeneity). Further potential endpoints (i.e., prevalence of patients who experience single or more than one thyroid event, autoimmune thyroid profile prior and after alemtuzumab, smoking habits, severity of hypothyroidism, and severity of GO) were not calculated due to the paucity of available data.

Study quality assessment

Concerning non-RCTs, the following were regarded as appropriate domains in each study: statement of the study aims; definition of study population; the absence of the outcome before the exposure; time frame between exposure and outcome; evaluation of outcome and follow-up periods. Since ALZ is commonly administered to hospital patients under strict medical supervision, exposure measures and assessment bias were judged absent. No explanations about sample size were reported. The relationship between the cumulative doses and/or the interval and/or the frequency of ALZ administration with outcome was reported in three studies [3, 14, 17]. Moreover, outcome measures were rated as accurate and reliable in each study. Only one study assessed the confounding variables (i.e., gender and smoking habits) [14]. Risk of bias summary for non-RCTs is depicted in Supplemental Fig. 1. Regarding the risk of bias in the four RCTs, data on random sequence generation were never reported, whereas only two studies used an interactive voice response system for allocation [15, 16]. Patients and personnel were not blinded in three papers, while no information was reported in the fourth [3]. Of note, as ALZ had adverse effects that precluded double-blinding, other types of study design would have been hardly feasible; indeed, in two RCTs, a rater-blinded protocol was planned [15, 16]. Finally, as, in each RCT, every predetermined outcome was reported in the pre-specified manner, the reporting bias was rated as low. Funding by a drug company was present in three RCTs [3, 15, 16] and this was judged as an overall and potential risk of bias. Risk of bias summary for RCTs' studies is depicted in Supplemental Fig. 2.

Discussion

Immune reconstitution after drug-induced lymphopenia is an immunologic event which has been observed following graft vs host reaction, active antiretroviral therapy, or alemtuzumab treatment for MS [1, 2, 5]. The thyroid gland represents the preferred target of autoimmune attack triggered by alemtuzumab during the reconstitution of the lymphocyte repertoire [1, 2]. Moreover, ATEs seem to occur almost exclusively when ALZ is used in patients affected by MS:

indeed, only anecdotal reports of ATEs after administration of ALZ are depicted in patients with other diseases (i.e., vasculitis and patients receiving cells and organs transplant) [19–21]; yet, no ATEs are described when high doses of ALZ are used in patients with CLL or rheumatoid arthritis [22]. Therefore, for reasons that remain unclear, MS is a favourable milieu where ALZ may trigger thyroid autoimmunity [2], so that thyroid dysfunction in alemtuzumab-treated MS patients represents a common challenge in clinical practice. Moreover, the current literature tell us that in this context, thyroid disorders can show clinical and immunological peculiarities [3, 4] and it is has been suggested that alemtuzumab-induced GD has a more favourable course than the conventional form [5, 6]. Thus, this topic appears worthy of a large-scale analysis, and in our study, we aimed to reach more robust evidence on prevalence, main features, and outcome of the spectrum of ALZ-induced autoimmune thyroid events in patients with MS.

ATEs' categories

The current paper is the first meta-analysis on this issue and it is based on a total of 1362 MS patients treated with ALZ arising from seven studies. We found that 487 patients with MS (all had a personal negative history for thyroid disease prior ALZ) experienced at least one episode of thyroid autoimmunity, representing the prevalence of 33% of patients among the cohort. Despite a very wide range interval of ATEs appearance (1 week up to 7 years), ATEs mostly occurred nearly 2,5 years after the last ALZ course: this peak time of ATEs appearance may coincide with the peak of reconstitution of B cells, which rise to 124% of baseline 27 months after ALZ [2]. Furthermore, when the data were available, they univocally agree that neither the cumulative dose nor the interval period or the frequencies administration of ALZ could influence the prevalence of ATEs. Concerning the clinical phenotype of thyroid dysfunction, GD was the most common disease being diagnosed in more than 60% of patients with ATEs, namely in ~ 20% of the cohort (95% CI, 17–26%). Approximately 0.5–3% of people develop Graves' disease during their lifetime [23] and similar percentages can be applied to MS population [24]: thus, an order of magnitude was smaller than that reported in the cohort of MS patients treated with alemtuzumab. Graves' hyperthyroidism typically manifested as overt dysfunction (mainly corresponding to cases needing therapy), while in the minority of cases as subclinical thyroid hyperfunction (85% and 11%, respectively). Moreover, GD was found to have a fluctuating course in a considerable proportion of cases (15% of patients with ALZ-induced GD). As shown in other settings [25], the described "pendulum swinging" of thyroid status observed in ALZ-induced GD fluctuations may depend on the proportion of TSH receptor-stimulating antibody (TSAb) and TSH receptor-blocking antibody (TBAb). As regards the ocular manifestations of Graves hyperthyroidism, we found a prevalence of about one out of ten patients with GD (lower than the 20% of GO associated with conventional GD [26]): however, since most patients with MS did not undergo routine ophthalmological assessment, this prevalence of GO could be underestimated. Furthermore, the incomplete data of the included studies prevented us from discriminating between mild and moderate or severe forms of GO and did not inform us about GO management. The second most frequent type of thyroid dysfunction was the hypothyroidism due to Hashimoto thyroiditis (characterized by positivity in TPOAb) which was developed by 15% of patients with ATEs, namely by the ~ 5% (95% CI 4–9%) of the cohort. The prevalence of hypothyroidism due to Hashimoto thyroiditis in the general population is around 5% in Europe [27], in line with what we found in MS patients treated with ALZ and also similar to what is reported for patients with MS [28]. Therefore, we speculate that an "antigenic preference" could explain the distinctive thyroid attack (towards Graves' versus Hashimoto's disease) in patients with MS treated with ALZ. Moreover, as patients serostatus (i.e., TPOAb and TRAb) before and during therapy was provided only by few papers (thus not permitting a statistical analysis), we could not investigate on the role of TPOAb and TRAb before alemtuzumab as a risk factor of ALZ-induced thyroid dysfunction, following on from what was suggested by Muller et al. [12]. However, although in the absence of conclusive evidence, in some countries, the autoimmune thyroid profile (and, specifically, TRAb) is already included in pre-alemtuzumab screening and alemtuzumab could not be administered in seropositive patients. Moreover, cases of silent thyroiditis (also named painless thyroiditis [29]) were registered in 9% of MS patients developing ATEs, while 2% was represented by hypothyroidism with positive TRAb (likely functioning as TBAb). The percentage of this latter category could be underestimated as in two of the included studies [16, 17]; we could not know if TRAb evaluation for primary hypothyroidism was homogeneously carried out.

Outcome and management of GD

In conventional Graves' disease, antithyroid drugs may determine remission in approximately 40–50% of patients treated for 12–18 months [30, 31], and a slightly higher proportion (56%) was found in our meta-analysis for ALZ-induced GD cases. Furthermore, to obtain disease control, 22% and 11% of patients with GD post-ALZ required additional definitive RAI and surgery, respectively. Severity and outcome of GD should be better examined by clinical tools. The GREAT and the CSS are the two main tools to assess the severity and the risk of relapse following drug withdrawal for Graves' disease [9]. According to the obtained GREAT

and/or CSS score, clinicians could move towards the most appropriate treatment (ATD therapy or definitive treatment by RAI or thyroidectomy) at diagnosis of Graves' hyperthyroidism [9]. In alemtuzumab-induced GD, the evaluation of the performance of GREAT and CSS tools (original or improved versions with additional factors, e.g., the fluctuating phenotype) should in future be pursued to validate their value in this new clinical scenario. Finally, we found that ~ 1 out of 10 patients with ALZ-induced GD (12%) likely went into remission spontaneously. Nevertheless, in these studies reporting cases of Graves' spontaneously remitted [3, 7] both the exact time (i.e., how many months after the diagnosis of GD) when spontaneous remission occurred and the uniformly TRAb measurement before making the final diagnosis of truly spontaneous remission were laking. Therefore, in this context, we cannot exclude that at least some cases of spontaneously remitted ALZ-induced GD could be only a transient event tied to the dynamic switching of circulating proportion of TBAb and TSAb. Long-term follow-up and serial TRAb measurement might actually answer on this issue. It should also be said that in conventional Graves' disease, the rate of spontaneous remission seems to be lower (~ < 5%) and some studies state that it may particularly take place after a lots of years from medical therapy (because the concomitant chronic thyroiditis induced failure of thyroid function) [32] or in cases of subclinical GD [33, 34].

Limitations

Some limitations of the current meta-analysis should be noted. First, we had too few data to provide conclusions about the relationship between some known risk factors (i.e., female gender, smoking habits, and positive thyroid autoimmune profile) and autoimmune thyroid disease development (i.e., GD) as well as to define the severity (overt or subclinical) of hypothyroidism and of GO. Second, there was moderate-to-high heterogeneity in some endpoints, something to be expected due to certain study characteristics (i.e., relatively small number of patients developing thyroid dysfunction with limited reporting of subgroup results, previous neurological treatments before ALZ, different patients' characteristics other than the extracted ones, and variable clinical practice patterns in the management of Graves' disease). Therefore, caution should be exercised when our findings will be used in clinical practice.

Conclusion

This meta-analysis revealed cogent evidence that the development of ATEs was a frequent complication after ALZ therapy, affecting more than three out of ten patients. ATEs mostly occurred after 2 years and some months from the most recent infusion of ALZ, but they have to be expected from some weeks to many years after therapy, so that a lifelong follow-up should be proposed. Among different categories of ATEs (including GD, HT, ST, and hypothyroidism with positive TRAb), Graves' hyperthyroidism was the most common thyroid dysfunction, occurring in more than half of patients developing ATEs. Yet, GD might exhibit a fluctuating course in a significant proportion of cases, and it typically manifested as overt hyperthyroidism with concomitant thyroid eye disease in at least one out of ten patients. Hypothyroidism due to HT was the second most common ATE and occurred with a similar frequency than general population and patients with MS. Since in the studies reporting data about GD management medical therapy were mostly adopted as first choice (namely, radioiodine or surgery after the attempt with thyrostatics) and as it could be effective in a half of patients to induce remission, our results should indirectly support to manage ALZ-induced GD patients with the first-line treatment consisting of antithyroid drugs. However, ALZ-induced GD could not be considered as having a more favourable outcome than conventional GD, as a major surveillance and/or an early definitive approach should be offered when a fluctuating and unpredictable thyroid status is observed.

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Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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