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REVIEW

Exploring autoimmune endocrine diseases induced by monoclonal antibodies used as multiple sclerosis pharmacotherapy: a systematic review

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Abstract
Multiple sclerosis (MS) is an autoimmune neurodegenerative disease that targets myelin, leading to inflammation and neuron death. Monoclonal antibodies (MAb) have long been used to control the progression and exacerbations of this disorder, which may induce secondary autoimmune disease as a rare adverse event. This systematic review aimed to gather data of case reports around this subject and to explain the mechanism behind their occurrence. PubMed, Scopus, and Google scholar were searched for published case reports until February 21st 2024. The Joanna Briggs Institute (JBI) critical appraisal checklist was used to assess the quality of the included studies. In total, 20 articles met the inclusion criteria and were reviewed by the authors. The most autoimmune disorders were thyroiditis and as expected induced by alemtuzumab. Ocrelizumab had one secondary autoimmune complication reported. MAbs used in MS immunotherapy have shown to induce secondary autoimmune disorders including endocrine complications, which have been reported in many case reports. It is recommended to use these agents with caution and monitor patients for symptoms of the aforementioned conditions.

Keywords Multiple sclerosis · Monoclonal antibody · Endocrine complications · Autoimmune disease

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by inflammation, demyelination, and neurodegeneration within the central nervous system (CNS), characterized by demyelination, axonal damage, and progressive neurological disability. MS typically manifests between the ages of 20 and 40, with a higher prevalence in women, and is recognized as the leading cause of non-traumatic disability among young adults (Ghiasian et al. 2021). While the exact etiology of MS remains elusive, it is widely accepted that genetic and environmental factors contribute to disease susceptibility and progression. Among the environmental factors, vitamin D deficiency, viral infections, and smoking have been implicated in the pathogenesis of MS (Abdollahzadeh et al. 2016; Poorolajal et al. 2017).

The efficacy and safety of disease-modifying therapies (DMTs) have garnered significant attention in MS management. While DMTs have revolutionized the treatment landscape for MS, their use is not without risk. Moreover, the efficacy of DMTs varies among individuals, and a substantial proportion of patients continue to experience disease progression despite treatment (Ghiasian et al. 2022). Recent studies have reported new adverse effects associated with therapies, underscoring the importance of post-marketing pharmacovigilance in optimizing patient care (Sahraian et al. 2022; Simbrich et al. 2021).

Among the various biological therapies used in MS management, alemtuzumab has drawn attention to its efficacy in reducing disease activity. However, it is associated with a spectrum of thyroid-related adverse events, including Graves' disease and orbitopathy, which can have significant clinical implications (Scappaticcio et al. 2020). Additionally, studies have identified risk factors and clinical characteristics associated with alemtuzumab-induced Graves' disease, providing insights into personalized risk stratification and preventive measures (Ueland et al. 2023).

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Given these challenges, there is an urgent need for more personalized therapeutic approaches and a deeper understanding of the disease mechanisms at the individual level. Although extensive research has been conducted on MS, critical gaps remain, particularly in identifying biomarkers for predicting treatment response and understanding the long-term effects of current therapies.

In light of the multifaceted nature of MS pathogenesis and management, this study aims to investigate the potential role of biological therapy in inducing autoimmune endocrine diseases in MS patients. By doing so, it seeks to contribute to developing of more tailored treatment strategies, ultimately improving outcomes for individuals living with MS.

Method

Data sources

This systematic review aimed to identify and analyze autoimmune endocrine disorders associated with DMTs used to manage MS attacks and progression. The review adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist guidelines. Searches were conducted in Google Scholar, PubMed, and Scopus databases for studies published up to February 2024.

Search strategy

The search strategy included the following terms: "multiple sclerosis," and (Natalizumab or Ocrelizumab or Rituximab or Alemtuzumab or Ofatumumab or Ublituximab), and (case report) and all MeSH terms in Pubmed Database. In Scopus, each monoclonal antibody AND "multiple sclerosis" was searched separately in Abstract/Title section and the total was added to the records. Google Scholar was searched for each monoclonal antibody AND "multiple sclerosis" separately; the total was then added. The selection of biologic drugs was based on therapies recommended by Wolters Kluwer's UpToDate®.

Eligibility criteria

The inclusion criteria for this study were as follows: (a) case reports or case series, (b) addressed the autoimmune endocrine complications of MS immunotherapy, (c) had a full text available. Records were excluded if they were (a) non-English or (b) complications other than endocrine disorders, (c) the review and meta-analysis studies, and letters to editors, clinical trials, and qualitative studies.

The authors agreed to refer to the Global Autoimmune Institute's Autoimmune Disease List (2024) to standardize disease categorization.

Data extraction

Endnote® 7 (Clarivate Analytics) facilitated screening and data extraction. Two researchers independently extracted data based on predefined criteria, with results reviewed by the remaining authors.

Quality assessment

The methodological quality of case report studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist, which includes eight Likert questions evaluating crucial aspects of case reports (Munn et al. 2020). These criteria assess the accuracy of patient demographic information, documentation of patient history, description of current clinical conditions, clarity of diagnostic and therapeutic measures, elucidation of post-therapeutic intervention outcomes, and identification and explanation of reported side effects. The overall utility of case reports was evaluated accordingly. See t 2 for detailed assessment criteria.

Results

A comprehensive search of the aforementioned databases up to February 21st, 2024, yielded 85 articles. After removing 58 duplicate articles, 27 unique articles underwent independent review by two researchers. Screening of titles and abstracts led to excluding additional six articles. Subsequently, the remaining articles underwent full-text assessment, resulting in the exclusion of no articles (see Fig. 1). Ultimately, 21 articles met the eligibility criteria.

These 20 articles provided data on 38 patients, with records primarily originating from Italy, Germany, and the UK, in descending order of prevalence. Additional records were sourced from Canada, Greece, Australia, Ireland, the USA, and Portugal. The summarized findings of these studies are presented in Table 1.

Of the eligible studies, 17 investigated autoimmune dermatologic complications associated with Alemtuzumab in MS patients, while two studies focused on Natalizumab and one on Ocrelizumab. Consequently, 38 patients across 20 studies examining three different biological therapies for MS were identified.

Alemtuzumab

Alemtuzumab, a monoclonal antibody that targets CD52, a protein on surface of B, T lymphocytes, monocytes and dendritic cells, has been utilized for chronic lymphocytic leukemia (CLL) and other lymphoid neoplasms (Katsavos and Coles 2018). Research has confirmed its effectiveness

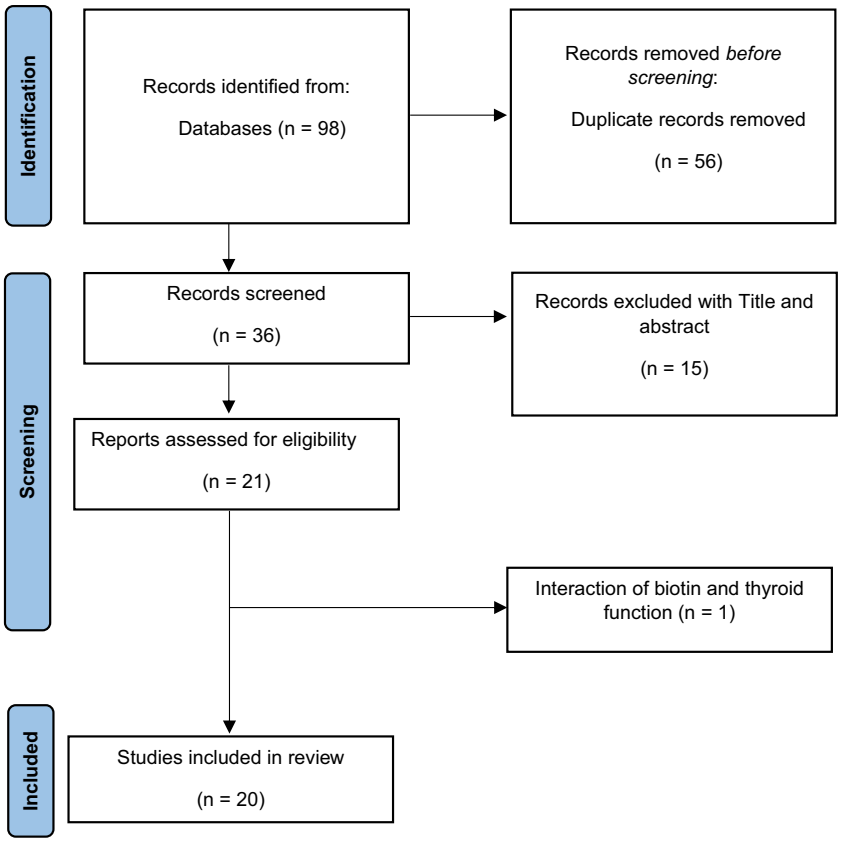

Fig. 1 Study selection process

in decreasing relapse rates of multiple sclerosis (MS) and disability progression, as well as its beneficial effects on radiological disease outcomes (Willis and Robertson 2016). However, its complications such as secondary autoimmune disease, necessitate careful monitoring and management (Cossburn et al. 2011).

Autoimmune complications

Alemtuzumab has been associated with many autoimmune complications, e.g., immune thrombocytopenia, hemolytic anemia, hepatitis, encephalitis, myasthenia gravis, Lambert–Eaton myasthenia, sarcoidosis, vitiligo, alopecia, myositis, and type 1 diabetes, but most prevalent reported is autoimmune thyroiditis by 33%, of which 63% were GD and 15% Hashimoto's. (Yue et al. 2023).

Research indicates that alemtuzumab can lead to prolonged lymphopenia and trigger secondary autoimmunity during the reconstitution of the lymphocyte repertoire. Cytokine signaling, e.g., increased Interleukin 21 and decreased IFN, also has been proposed to play a role (Conway 2022). Patients with high baseline levels of Interleukin21 are at a higher risk of developing autoimmune conditions post-treatment with alemtuzumab (Ruck et al. 2022; Costelloe et al. 2012). The incidence of thyroid dysfunction in the first 3 years rises each year (Alamo et al. 2019). This typically tends to resolve on its own in approximately 30% of cases, possibly attributed to a higher frequency of neutralizing or blocking TRAb. (Moli et al. 2021).

Natalizumab

Natalizumab is a monoclonal antibody used to treat RRMS (Hutchinson 2007). Natalizumab inhibits the interaction between the integrin alpha subunit of VLA-4 on leukocytes and VCAM-1, which is vital in regulating immune and inflammatory responses. Research indicates that the VLA-4 and VCAM-1 pathways may be significant in the autoimmune response seen in autoimmune thyroid disorders (Marazuela et al. 1994; Nakashima et al. 1994).

Autoimmune complications

Natalizumab has been associated with the development of autoimmune hepatitis, immune thrombocytopenic purpura, and rheumatoid arthritis (Lisotti et al. 2012; Stosic et al. 2011; Su et al. 2020). Some theories suggest that Immune Reconstitution Syndrome (IRS) plays a role (Carcelén-Gadea et al. 2013; Metz et al. 2012) and also inducing a shift towards a Th17-mediated inflammatory response while blocking Th1 cell entry can be an explanation (Su et al. 2020). However, additional research is necessary to fully

Table 1 Case report studies of endocrine autoimmune disease induced by MS monoclonal antibodies

Drugs	Study	Type of autoimmunity	Medical history	Timeline of accused drug utilization/ Management	Lab findings		Outcome	Age/Gender
Alemtuzum ab	(Alamo et al. 2019)	Autoimmune thyroid disease	RRMS/ IFN Positive family history for hypothyroidism	18 months after 2nd infusion/ propranolol then levothyroxine	TSH (0.34–4.2 mUI/L)	0.0	Followed hypothyroidism	37/F
						43.97		
					TgAb(< 4 IU/mL)	196		
					TPOAb(< 9 IU/mL)	482		
	(Obermann et al. 2016)	Autoimmune thyroid disease and ITP	RRMS since 2011/ IFN beta 1a/ fingolimod Mother history of GD	11 months after 1st infusion/ carbimazole	TSH(0.3–3 µU/mL)	< 0.01	Stable/ Not continued	26/M
					TgAb (< 40 U/mL)	688		
					TSHRAb (< 1.75 U/L)	4.95		
					TPOAb(< 35 U/mL)	185		
	Obermann et al. 2016)	Autoimmune thyroid disease and ITP	RRMS since 2004/ IFN beta 1b/ fingolimod	9 months after 1st infusion/ no clinical symptoms	TgAb (< 60 U/mL)	315.7	Continued to 2nd dose	28/M
					TPOAb(< 60 U/mL)	589.3		
	(Aranha et al. 2013)	Autoimmune thyroid disease	3 years of RRMS	55 months after 1st infusion/ carbimazole	TSH (0.34–5.6 mIU/L)	< 0.05	NM	40/F
					TRAb (< 1.5 IU/L)	2.6		
					TPOAb(< 60 IU/L)	104		
					TgAb(< 60 IU/L)	231		

Table 1 (continued)

Drugs	Study	Type of autoimmunity	Medical history	Timeline of accused drug utilization/ Management	Lab findings		Outcome	Age/Gender
	Aranha et al. 2013)	Autoimmune thyroid disease	7 years of RRMS/ IFN beta1b	39 months after 1st infusion/ carbimazole then levothyroxine	TSH (0.34–5.6 mIU/L)	< 0.05	Stable	53/F
					TRAb (< 1.5 IU/L)	270		
	Aranha et al. 2013)	Autoimmune thyroid disease	3 years of RRMS/ asthma	27 months after 1st infusion/ carbimazole and propranolol	TSH (0.34–5.6 mIU/L)	< 0.05	Subtotal thyroidecto my	36/F
					TRAb (< 1.5 IU/L)	88		
	Aranha et al. 2013)	Autoimmune thyroid	10 years of RRMS/ smoker/	14 months after 1st	TSH (0.34–5.6 mIU/L)	< 0.05	Subtotal thyroidecto	46/F
		disease	IFN beta1b	infusion/carbimazole	TRAb (< 1.5 IU/L)	26	my	
					TPO(< 60 IU/L)	83		
					TgAb(< 60 IU/L)	188		
	Bianco et al. 2020)	Sever GD and febrile neutropenia	RRMS at 25/ interferon and fingolimod	One year after 2nd dose/ Methimazole	TSH (0.35–3.2)	Base:1.45 µIU/mL)	Urgent thyroidecto my	33 /F
						0.01 µIU/mL		
					TgAb (< 60)	173.4 µIU/mL		
						Relapse: > 500 µIU/mL		
					AbTPO(< 60)	Relapse:535.4 µIU/mL		
					TRAb(< 0.57)	11.5 µIU/mL		
						Relapse > 40 µIU/mL		

Table 1 (continued)

Drugs	Study	Type of autoimmunity	Medical history	Timeline of accused drug utilization/ Management	Lab findings		Outcome	Age/Gender
	Conway 2022)	GD	MS at 25/ interferon β1a and fingolimod Depression	At 35 switched to alemtuzumab and after 1 year diagnose with GD/Carbimazole + propranolol	TSH	< 0.01 mU/L	Improved	37/F
	Garrahy et al. 2019)	Hyperthyroidism	RRMS/GA 12 weeks	15 months after infusion/ carbimazole	TRAb (0–1.5 IU/L)	15.2	Thyrotoxicosis in neonate/ fluctuated thyroid function	36/F
	Daraki et al. 2021)	GD and concurrent immune thrombocytopenia	RRMS since 2009 Albinism Positive family history of thyroid dysfunction and arthritis rheumatoid	21 months after 3 courses of alemtuzumab/ thamazole + propranolol	All TgAb, TPOAb, TSI were positive		Followed hypo and hyperthyroidism alternating phases	27/ F
	Moli et al. 2021)	Marine-Lenhart syndrome and Graves' ophthalmopathy	MS for 3 years/ At 2017 subclinical hyperthyroidism	after 5 months of initial alemtuzumab/ methimazole + selenium	TSH	Base:0.2 mU/L	Improved with medication/ Continued to 2nd dose but worsened GD symptoms	36/F
						2018:0.08 mU/L		
						After 2nd dose: absent		
						After therapy: < 0.01 mU/L		
					TRAb (< 1.5 U/L)	After 2nd dose: 21.5		

Table 1 (continued)

Drugs	Study	Type of autoimmunity	Medical history	Timeline of accused drug utilization/ Management	Lab findings		Outcome	Age/Gender
	Mahzari et al. 2015)	Thyroid disease	RRMS	12 months after 2nd infusion/ PTU then levothyroxine	TPOAb positive/ RAIU(6–22%) 33%		Changed to hypothyroidism/ NM	49 /M
	Mahzari et al. 2015)	Thyroid disease	RRMS	5 months after 2nd infusion/ propranolol then levothyroxine	TPOAb positive		Changed to hypothyroidism/ NM	37/F
	Mahzari et al. 2015)	GD	RRMS/ family history hypo- and hyperthyroidism	16 months after 2nd infusion/ methimazole + metoprolol	TPOAb positive/ RAIU(6–22%) 58.7%		Improved/ NM	34/F
	Mahzari et al. 2015)	Subclinical Thyroid disease	RRMS	9 months after 2nd infusion	Low TSH		Changed to symptomatic hypothyroidism/ NM	34/F
	Tsourdi et al. 2015)	GD	MS since 2006 / IFN beta 1b/ HTN/ smoker	28 months after 1st infusion/ also positive insulin Ab /thiamazole + propranolol	TSH (0.3–4.2 mU/L)	< 0.01	12 months of pharmacotherapy/ NM	35/M
					TSHRAb (< 1U/L)	8		
					TPOAb(< 60 U/mL)	> 3000		
					TgAb(< 60 U/mL)	89		
	Tsourdi et al. 2015)	GD	MS since 2006/IFN beta 1b	38 months after 1st infusion/ thiamazole + propranolol	TSH (0.3–4.2 mU/L)	< 0.01	Total thyroidectomy/NM	31/F
					TSHRAb (< 1U/L)	12		
					TPOAb(< 60 U/mL)	93		
					TgAb(< 60 U/mL)	89		

Table 1 (continued)

Drugs	Study	Type of autoimmunity	Medical history	Timeline of accused drug utilization/ Management	Lab findings		Outcome	Age/Gender
	Tsourdi et al. 2015)	GD	MS since 2004/ smoker	28 months after 1st infusion/patchy alopecia/ thiamazole	TSH (0.3–4.2 mU/L)	< 0.01	Total thyroidectomy/NM	34/F
					TSHRAb (< 1U/L)	39		
					TgAb(< 60 U/mL)	73		
	Tsourdi et al. 2015)	GD	MS since 2007/IFN beta 1a/ smoker	23 months after 1st infusion/ thiamazole + propranolol	TSH (0.3–4.2 mU/L)	< 0.01	Total thyroidectomy/NM	38/M
					TSHRAb (< 1U/L)	22		
					TPOAb(< 60 U/mL)	> 3000		
	Tsourdi et al. 2015)	Subclinical GD	MS since 2006/ IFN beta 1a/ Anxiety disorder	44 months after 1st infusion/ no treatment	TSH (0.3–4.2 mU/L)	< 0.01	NM	47/F
					TSHRAb (< 1U/L)	3		
					TPOAb(< 60 U/mL)	489		
					TgAb(< 60 U/mL)	962		
	Malmeström et al. 2014)	Type 1 diabetes	MS at 32/ IFN beta 1a Father type 2 diabetes Mother and sister hypothyroidism	17 months after 2nd infusion GD/thiamazole 29 months after 2nd infusion DM1/Insulin	Pre-treatment and 12 months after 2nd infusion ICA, GAD antibodies positive 29 months after 2nd infusion, ICA, GAD, IA-2, ZnT8 antibodies positive. Fasting p-glucose (4.2–6.3 mmol/L) 19		Thyroidectomy	34 /F
	Richter et al. 2019)	Type 1 diabetes	RRMS at 19/ IFN and Natalizumab Mother had MS	14 months after 2nd infusion both DM1 and thyroiditis / Insulin and levothyroxine	Blood glucose 540 mg/dL and urine glucose > 500 mg/dL Positive GAD antibody TSH (0.35–3.5μU/mL) 15.6 TPOAb(< 35 IU/mL) > 950 TgAb (< 3.9 IU/mL) 877		NM	37/M

Table 1 (continued)

Drugs	Study	Type of autoimmunity	Medical history	Timeline of accused drug utilization/ Management	Lab findings		Outcome	Age/Gender
	Richter et al. 2019)	Type 1 Diabetes	RRMS at 13/IFN Epilepsy	10 months after 1st infusion thyroiditis/ levothyroxine 10 months after 2nd infusion DM1/Insulin	TSH (0.35–3.5µU/mL) 260 TPOAb(< 35 IU/mL) 241 TRAb 25 IU/L		NM	25 /F
	Roos et al. 2019)	Immune reconstitute on triggering Graves' orbitopathy	MS since 26/ IFN beta 1a	12 months after 4th infusion/ carbi mazole and thyroxine	TSH(0.35–5.5 mU/L)	< 0.03	Slight improvement/Not continued	36/M
					TPOAb	54 IU/L		
					TRAb (< 1 IU/L)	> 40		
	Roos et al. 2019)	Immune reconstituti on triggering Graves' orbitopathy	MS at 41/ IFN beta 1a/ Smoker	7 months after 2nd dose/ NM	TSH(0.35–5.5 mU/L)	< 0.03	Normalized lab test/ Not	47/M
					TPOAb	> 1300 IU/L	continued	
					TRAb (< 1 IU/L)	29		
	Roos et al. 2019)	Immune reconstituti on triggering Graves' orbitopathy	MS at 14/ IFN beta 1a/ Ex-smoker	1 year after initiation/ radioiodine ablation	TSH(0.35–5.5 mU/L)	0.19	NM/ continued	39/M
					TPOAb	> 1300 IU/L		
					TRAb (< 1 IU/L)	22.5		

Table 1 (continued)

Drugs	Study	Type of autoimmunity	Medical history	Timeline of accused drug utilization/ Management	Lab findings		Outcome	Age/Gender
	Roos et al. 2019)	Subclinical Hypothyroidism then Hashimoto's	MS at 46/ smoker	10 months after 1st infusion/ thyroxine	TSH(0.35–5.5 mU/L)	12.4	Managed/ Continued	46/M
					TPOAb	> 1300 IU/L		
					TRAb (< 1 IU/L)	15.9		
	Roos et al. 2019)	Immune reconstituti on triggering Graves' orbitopathy	MS at 43	2 years after 1st infusion/ radioiodine ablation	TSH(0.35–5.5 mU/L)	6.3	NM/Not continued	54/F
					TPOAb	1378 IU/L		
	Roos et al. 2019)	Immune reconstituti on triggering Graves' orbitopathy	MS at 46	2 years after 2st infusion/	TSH(0.35–5.5 mU/L)	< 0.03	Total thyroidectomy/	54/F
					TPOAb	< 5 IU/L	Not continued	
					TRAb (< 1 IU/L)	> 40		
	Thakar et al. 2019)	GD hyperthyroidism	GA 28 week	22 months after / PTU	TSH	0.03 mU/L	Carbimazole for the neonate	27 /F
					TRAb (0-1 IU/mL)	> 40		

Table 1 (continued)

Drugs	Study	Type of autoimmunity	Medical history	Timeline of accused drug utilization/ Management	Lab findings		Outcome	Age/Gender
	Yue et al. 2023)	hyperthyroidism secondary to GD and chronic thyroiditis	PPMS since 25/ fingolimod MDD, PTSD, cannabis use disorder	At 27–28 natalizumab, At 32 started alemtuzumab/ atenolol and methimazole	TSH (0.35–5 U mL)	Base:0.89	Thyroidectomy/ Alemtuzumab discontinuation	37 /M
						At 34: 0.01		
					TSI (< 140%)	208%		
					TPO (< 9 IU/mL	701		
	Nirmalan et al. 2023)	GD with eye complicati ons	13.8 years of MS/ 4 were smokers	42.2 months after alemtuzumab developed GD	TSH	0.28 IU/L	3 thyroidectomy and 4 used thioamides/ NM	43.8 (2 M and 3 F)
					TSI (< 0.54 IU/L)	79.9		
					TRAb (< 1.75 IU/L)	10.1		
					TPOAb(< 34 IU/L)	2.123		
	Trinh et al. 2016)	Thyroid eye disease	3 years of MS until diagnosis	Almost 2 year after 1st infusion	TSHRAb(< 1.8 IU/L)	17–33.9 (peak 88)	thyroidectomy	36/F
Natalizumab	Oddo et al. 2014)	Thyroiditis	Natalizumab since 2010	2 months after initiation/ predn isolon + propranolol	TSH (0.3–4.2 mU/L)	Base: 2.72	Improved/ continued	28 / F
						0.03		
					TPOAb (0-100 mU/L)	290–380		

Table 1 (continued)

Drugs	Study	Type of autoimmunity	Medical history	Timeline of accused drug utilization/ Management	Lab findings		Outcome	Age/Gender
	Carcelén-Gadea et al. 2013)	Transient autoimmun e hyperthyro idism after withdrawal	MS since 2008/ Subclinical hyperthyroidism on Interferon beta 1a Mother positive for thyroid disease	3 months after withdrawal of 3.5 years of natalizumab	TSH (0.34–	On IFN: 0.01	Spontaneous/ continued	28 /F
					5.6 mcUI/mL	0.03		
					TPOAb (0-9UI/mL)	On IFN: 59.1		
						91.1		
					TgAb (0–4 UI/mL)	On IFN: 185–450		
						219.1		
	Carcelén-Gadea et al. 2013)	Transient autoimmun e hyperthyroidism after withdrawal	MS since 2009/ Subclinical hypothyroidism on Interferon beta 1a Sister positive for hypothyroidism	3 months after withdrawal of 18 months of natalizumab	TSH (0.34–5.6 mcUI/mL	On IFN: 6.71	Spontaneous/ discontinued	32 /F
						0.08		
					TPOAb (0-9UI/mL)	237.5		
Ocrelizumab	(Duarte et al. 2021)	[Subclinical] GD	PPMS since 2007	6 months after 1st dose/ surveillance	TSH (0.27–4.288µUI/mL)	Base:1.88	Spontaneous/ continued biannually	59/ F
						0.02–0.04		
					TRAb(< 1.22 U/L)	36.5		
					TPOAb (< 34 UI/mL)	> 600		

understand the mechanisms and potential risk factors for these complications.

Ocrelizumab

Ocrelizumab, a second-generation humanized antibody that targets the CD20 antigen expressed by a vast range of B cells and about 5% of T cells, has been approved for the treatment of RRMS and primary progressive MS (Duarte et al. 2021; Lünemann et al. 2020). Main complications of ocrelizumab-therapy have been infusion-related reactions and infections (Montalban et al. 2017).

Autoimmune complications

Increased risk of developing psoriasis and inflammatory bowel disease has been reported by ocrelizumab administration (Lamb 2022). Also, glomerulosclerosis and Graves' disease have been reported in some case reports (Duarte et al. 2021; Greve et al. 2023). Some hypotheses state there may be an association with B cell depletion immune system dysregulation (Lee et al. 2020) (Table 2).

Discussion

This study aims to explore the mechanisms underlying biological therapy-induced autoimmune endocrine diseases in MS patients as is summarized in Table 3. By elucidating the underlying pathophysiology, pictured in Fig. 2 and identifying at-risk patient populations, this research seeks to inform personalized treatment strategies and enhance the safety and efficacy of MS management.

To our knowledge, this is the first systematic review of case reports on secondary autoimmune endocrine disorders induced by multiple sclerosis immunotherapy monoclonal antibodies.

We reviewed 20 articles that met the inclusion criteria (3 America, 16 Europe, and 1 Australia). Seventeen studies involved Alemtuzumab with a total of 34 patients who developed autoimmune endocrine complications; two studies included Natalizumab with 3 patients suffering from its endocrine adverse effects. One study contributed to Ocrelizumab endocrine complications, with one patient experiencing the side effects of this drug. A total of 38 patients had experienced induced autoimmune endocrine side effects.

A systematic review and meta-analysis highlight the prevalence and clinical characteristics of alemtuzumab-induced thyroid events in MS patients, emphasizing the importance of vigilant monitoring and early intervention (Scappaticcio et al. 2020). This aligns with findings by other studies, which have consistently demonstrated the necessity for proactive management of thyroid dysfunction in this patient population due to the autoimmune risks associated with immune reconstitution therapies (IRT). Additionally, it was hypothesized in the same article that there is an antigen preference of TRAb in MS patients treated with alemtuzumab, suggesting a specific immunological shift linked to the therapy.

Interferons, which have been used as a pharmacotherapy for MS, have long been associated with thyroid complications and one of the stated theories proposes their indirect immune-mediated action, pro-inflammatory cytokines increase, inhibition of regulator T cells and switching to immunological Th1 pattern (Tomer and Menconi 2009). This mechanistic insight is crucial for understanding the broader context of immune responses in MS therapies. Development of immune reconstitution therapies, including antibody-based cell depletion therapies, targeting CD52 + (alemtuzumab) or CD20 + (ocrelizumab) leukocytes (Kazakou et al. 2023), through short-term intense immunosuppression or immune cell depletion, rebuilds an immune system with freshly built immune tolerance (Lünemann et al. 2020).

The majority of immune reconstitution autoimmune diseases post-alemtuzumab treatment of MS have been theorized to be antibody-dependent; however, type 1 diabetes is the result of pancreas cell destruction by self-reactive T cells. Therefore, Malmetrom et al. suggest that post-alemtuzumab secondary autoimmune conditions are not confined to be mediated by autoantibody (Malmeström et al. 2014).

A study on cardiac transplantation indicated that induction therapy with alemtuzumab may result in a lower incidence of new onset diabetes, suggesting a complex relationship between alemtuzumab and diabetes across different medical contexts. However, it was suggested that lower need of corticosteroid post transplantation can be the possible etiology (Jones et al. 2010). This finding contrasts with the higher incidence of autoimmune conditions in MS patients, highlighting the need for disease-specific investigations into the drug's effects.

The associated thyroid dysfunction related to IRT has been characterized as delayed onset with transient dysfunction and spontaneously resolved. Also, although conventional GD is thought to be induced by humoral immunity, T cells are at function in this case (Muller et al. 2018). During immune reconstitution autoimmunity, Th2 profile cytokines are replenished to greater extent, making Th1 mediated disorders like Hashimoto's thyroiditis less common (Weetman 2009). Interestingly, MS progression is also derived by Th1 phenotype (Conway 2022).

Although alemtuzumab causes depletion of B and T lymphocytes (including CD8 + and CD4 +); recovery of B cell counts occurs earlier (by 3 to 6 months) while T cell counts, especially CD4 +, remain low even after 12 months. Overpopulation of B cells (127% of their base level at 27th months (Roos et al. 2019)), in the absence of regulatory T

Table 2 JBI critical appraisal checklist for case reports

Author	Were patient s demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Overall appraisal
(Yue et al. 2023)	Y	Y	Y	Y	Y	Y	Y	Y	Include
(Nirmalan et al. 2023)	Y	Y	Y	Y	Y	UC	Y	Y	Include
(Conway 2022)	Y	Y	Y	Y	Y	UC	Y	Y	Include
(Le Moli, Russo et al. 2021)	Y	Y	Y	Y	Y	Y	Y	Y	Include
(Daraki et al. 2021)	Y	Y	Y	Y	Y	Y	Y	N	Include
(Bianco et al. 2020)	Y	Y	Y	Y	Y	Y	Y	Y	Include
(Thakar et al. 2019)	Y	N	Y	Y	Y	Y	UC	Y	Include
(Malmeström et al. 2014)	Y	Y	Y	Y	Y	Y	UC	Y	Include
(Richter et al. 2019)	Y	Y	Y	Y	Y	N	Y	Y	Include
(Aranha et al. 2013)	Y	Y	Y	Y	Y	Y	Y	Y	Include
(Garrahy et al. 2019)	Y	Y	Y	Y	Y	N	Y	Y	Include
(Alamo et al. 2019)	Y	N	Y	Y	Y	Y	Y	Y	Include
(Roos et al. 2019)	Y	Y	UC	Y	Y	Y	Y	Y	Include
(Obermann et al. 2016)	Y	Y	Y	Y	Y	Y	Y	Y	Include
(Mahzari et al. 2015)	Y	Y	Y	UC	N	Y	Y	Y	Include
(Trinh et al. 2016	Y	Y	Y	Y	Y	Y	Y	Y	Include
(Tsourdi et al. 2015)	Y	Y	Y	N	Y	UC	Y	Y	Include
(Carcelén-Gadea et al. 2013)	Y	Y	Y	Y	Y	Y	Y	Y	Include
(Oddo, Laroni et al. 2014)	Y	N	Y	Y	Y	Y	Y	Y	Include
(Duarte et al. 2021)	Y	Y	Y	Y	Y	Y	Y	Y	Include

Table 3 Different proposed mechanisms behind endocrine complications of MS monoclonal antibodies

Agents	Disorder	Findings and Proposed Pathogenesis
Alemtuzumab	Thyroid disease	Quick/complete recovery of B cell levels(6–12 months), opposed to the slower/partial recovery of T cell (30–61 months)(14), during reconstitution phase, and thus enhanced production of autoantibodies. (Daraki et al. 2021) No regulation by CD4 + T-cell on naive B cells (Conway 2022). (Shown in Fig. 2A) Reconstituted CD8 + T cells may have low threshold to self-antigens, less relying on co-stimulatory signalling, bottlenecked and oligoclonal (Conway 2022) Lymphocytes (T cells (Obermann et al. 2016)) escaped from cytolysis undergo homeostatic proliferation (possibly Interleukin 21 driven (Obermann et al. 2016)), setting up a self-oriented and exaggerated response (Daraki et al. 2021) (predominantly by oligoclonal, highly proliferative, and chronically activated effector memory T cells (Obermann et al. 2016))(Shown in Fig. 2B) Faster recovery of CD8 + T cells, and a reduced production of memory CD4 + T cells. (Aranha et al. 2013) Increased T cell apoptosis and cell cycling influenced by interleukin 21 (Aranha et al. 2013) Genetic predisposition + lymphopenia + higher propensity of T lymphocyte apoptosis (Tsourdi et al. 2015) Dysbalance of regulatory T cell interrupts their immunomodulatory properties and ease the pro-inflammatory actions of Th1 and Th2 cells (Th1 suppression and decrease Th1/Th2 ratio (Aranha et al. 2013)), having a permissive effect on the production of TSHRAb (Tsourdi et al. 2015)(Shown in Fig. 2C) High levels of Interleukin-21 in MS patients and said cytokine receptor-positive T-cell, answering to self-antigens (Tsourdi et al. 2015) Lymphocyte depletion by neutrophils and NK-cell in the periphery, therefore lowering their number in thyroid and facilitating local autoimmunity (Tsourdi et al. 2015)(Shown in Fig. 2D)
	Type 1 diabetes	Islet destruction by autoreactive T cell after immune reconstitution (Malmeström et al. 2014)
Natalizumab	Thyroid complications	After discontinuation of natalizumab, emergence of immune reconstitution syndrome in predisposed individuals who have positive family history of thyroid disease or have had interferon-therapy (Carcelén-Gadea et al. 2013) Direct toxicity on thyroid tissue or blood supply, as pure destructive thyroiditis or an effect of immune system (Oddo et al. 2014)
Ocrelizumab	GD	Breakdown of immune tolerance and failure to detect anti-TSH-receptor T cell and B cell, self-reactive T-CD4 + and T-CD8 +, also hyper population of immature and transitional B cell (Duarte et al. 2021)

cells, and overpopulation of naive B cells with prolonged depletion of memory B cells is the possible cause for the secondary autoimmunity of B cells that may occur with alemtuzumab treatment.

This pathophysiology requires the involvement of T cells. It is therefore less likely to occur until CD4 + T cell numbers reach a sufficient level, leading to a delay between hyperreactivity of B-lymphocytes and the development of autoimmunity. Furthermore, T cell reconstitution is primarily due to peripheral expansion (rather than thymic reconstitution), promoting self-reactive immune cell populations (Sellner and Rommer 2020).

Ocrelizumab, on the other hand, B cell and CD20 + T cell are depleted while CD4 + and CD8 + T cells levels do not change (Sellner and Rommer 2020). Repopulation of B cells is preferentially achieved by immature or transitional B cells and myeloid cells following anti-CD20 + treatment have an enhanced activation state and proinflammatory differentiation (Häusler et al. 2018). These differences in immune reconstitution mechanisms between alemtuzumab and ocrelizumab highlight the necessity of drug-specific monitoring protocols to mitigate the risk of secondary autoimmunity.

Secondary autoimmunity following treatment with alemtuzumab has been noted in individuals with MS, but it has not been observed in cancer or rheumatoid arthritis patients. It has been suggested that cytokine signaling or lymphocyte function specific to MS patients might enhance the development of autoimmunity after immune reconstitution. However, no such enhancing factors have been identified thus far (Conway 2022). The balance between Th1 and Th2 and the derivation from the original phenotype in each individual might be the main factor.

It has been suggested in another article (Carcelén-Gadea et al. 2013) that after discontinuation of natalizumab, a self-limited autoimmune thyroid disorder may emerge as a presentation of IRS in predisposed individuals who have a positive family history of thyroid disease or have had interferon therapy, as use of natalizumab appears to control the immune response against the thyroid, with implications for post-therapy monitoring strategies.

Homeostatic proliferation commonly refers to the expansion of peripheral T cells in situations of lymphopenia. In lymphoreplete settings, low-affinity interactions between the major histocompatibility (MHC)/peptide complex and T cell receptor (TCR) in the periphery provide continuous

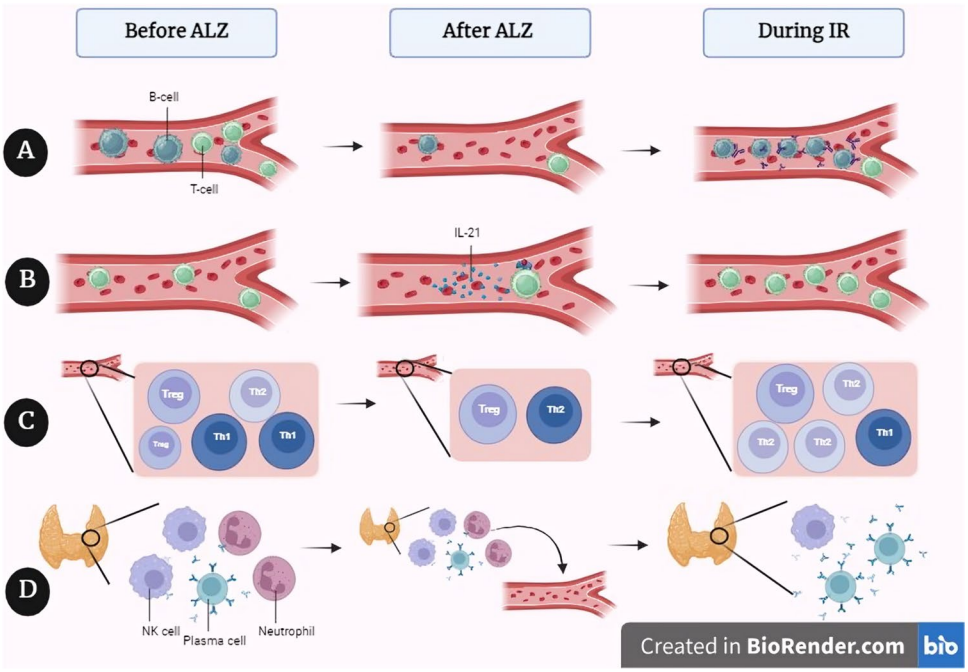

Fig. 2 Different pathophysiology behind developing Graves' disease in alemtuzumab-treated patients

"survival signals" to naïve T cells without triggering proliferation. Conversely, in cases of lymphopenia, these signals prompt T cell proliferation, to the level of homeostatic proliferation is directly linked to the extent and duration of lymphopenia. Consequently, homeostatic proliferation selectively amplifies T cells with a heightened specificity and stronger avidity for self-antigens. This process may contribute to the development of autoimmunity triggered by lymphopenia, as observed with alemtuzumab and other depleting agents (Aranha et al. 2013).

Rituximab is an old generation of CD20 + targeting monoclonal antibodies which have been used in treatment of Graves' orbitopathy but thyroid function levels have not been affected when using this drug (Salvi et al. 2015). The remaining non-CD20 + expressing plasma cells releasing autoantibodies can be the explanation (Duarte et al. 2021). Also, this agent, based on its mechanism of action, has been proposed to be administered as a protective agent, lowering the population of naïve B cell in reconstitution phase to lower the incidence of post-alemtuzumab GD autoimmunity (Conway 2022).

Smoking is one of the risk factors for developing thyroid complications post-alemtuzumab and sex distribution unlike dominant female prevalence in MS and GD is equal in this case (Nirmalan et al. 2023). Alemtuzumab dose, frequency, and interval have not appeared to be a risk factor (Trinh et al. 2016). In autoimmune thyroid disease, androgen-mediated reduction in thyroid cells expression of HLA-I and -II antigens have been suggested as a potential mechanism. Additionally, females are known to have an immune response with dominance of Th2, leading to enhanced B cell activation and production of autoantibodies (Tsourdi et al. 2015). Also it has been suggested that TSHRAb production by increased counts of memory-like T lymphocytes is more outstanding and more sustained in alemtuzumab induced thyroid disease than conventional cases (Tsourdi et al. 2015).

Also findings of Rolla et al. emphasize that alemtuzumab leads to a long-lasting reduction in CD4 + T cell counts, with Treg cell playing a crucial role in maintain long-term immune regulation and potentially mitigating some autoimmune responses (Rolla et al. 2022).

Conclusion

Multiple sclerosis (MS) presents significant management challenges due to its complex nature and the evolving landscape of treatment options. To optimize patient care, clinicians should consider enhancing clinical education, adopting a multidisciplinary approach, implementing routine monitoring, and developing personalized care plans.

For future research directions, we suggest conducting longitudinal studies to explore the long-term impact of novel MS treatments, risk factors and prognosis, and prioritizing patient-centered outcomes.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT 3.5 in order to enhance the grammar and presentation of this article. After using this tool/service, the authors

reviewed and edited the content as needed and take full responsibility for the publication's content.

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Authors' contributions A.S. conceptualized the subject of the manuscript, supervised the process and revised the manuscript. S.E. searched the database and was a major contributor in writing the manuscript. SA constructed the methodology, gathered and analyzed the chosen articles. NG prepared the original draft. All authors read and approved the final manuscript. The authors confirm that no paper mill and artificial intelligence was used.

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Declarations

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