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New autoimmune disorder development after immune reconstitution therapy for multiple sclerosis

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Immune reconstitution therapy (IRT) is a relatively new and highly effective treatment option for multiple sclerosis (MS). Uncertainty regarding the development of autoimmune disorders (ADs) after some therapies remains. The aim of this study was to assess new AD development after IRT in MS patients and to describe the nature of those ADs and the time to onset. A total of 179 patients with relapsing multiple sclerosis (37 after autologous haematopoietic stem cell transplantation (AHSCT), 19 after alemtuzumab (ALE) and 123 after cladribine (CLA) treatment) over a ten year period were included in the study. ADs were observed in 6 patients (16.2%) after AHSCT, 8 patients (42.1%) after ALE and 2 patients (1.6%) after CLA treatment. ADs developed earlier after ALE infusions, but later after AHSCT except for cytopenias. Neurologists should be attentive to the development of secondary ADs after ALE and AHSCT in MS patients.

Keywords Relapsing multiple sclerosis, Immune reconstitution therapy, Autoimmune disorder, Autologous haematopoietic stem cell transplantation, Alemtuzumab, Cladribine

Immune reconstitution therapy (IRT) is a form of high-efficacy treatment for relapsing multiple sclerosis (RMS) that has the potential to induce long-term or even permanent drug-free remission in people with multiple sclerosis (MS)[1,2]. These therapies deplete components of the immune system with the aim of allowing the immune system to renew itself. Cladribine (CLA), which is orally administered in two yearly treatment courses, and the monoclonal antibody alemtuzumab (ALE), which is administered by intravenous infusions for two yearly treatment courses are frequently categorized as IRT[3,4]. Autologous haematopoietic stem cell transplantation (AHSCT), which has been commonly used for a long time for the treatment of haematological cancers, is also increasingly used for the treatment of patients severely affected by autoimmune diseases, including MS[5]. AHSCT could be considered the strongest IRT for MS[2,6]. AHSCT induces ablation of the immune system via the removal of inflammatory and autoreactive cells and results in immunosuppression that is relatively short and depends on the intensity of the conditioning regimen[7–9]. Some drugs may be difficult to place according to the MS disease-modifying therapy (DMT) classification; for example, anti-CD20 depleting therapies might also have some characteristics of IRT, as they modify the immune cell profile upon reconstitution[1,7].

IRT is a new treatment option for MS, which is an autoimmune disease; however, some data have shown that IRT can potentially induce secondary autoimmune diseases (ADs)[10–13]. Secondary ADs were first described after haematopoietic stem cell transplantation (HSCT), mostly after allogenic procedures, which were undertaken for haematologic diseases[12,13]. Thyroid disorders are the most common endocrine disorders occurring after transplantation[14,15]. However, the incidence rate of thyroid dysfunction after HSCT was calculated in the population with different disorders treated with HSCT and different conditioning regimens, even in those patients in whom ALE was used for the conditioning regimen[16]. Some of the other most common autoimmune diseases after HSCT include autoimmune cytopenias, which can occur in up to 5–6% of patients. Among them, autoimmune thrombocytopenia is the most common and occurs in 2% of patients treated with AHSCT[12,13,16–20].

ALE is considered a highly effective disease-modifying therapy for RMS. However, its utility is limited because it increases the risk of infections and, in particular, secondary ADs. The current perspective suggests that ALE profoundly alters the circulating lymphocyte phenotype and describes a reconstituted immune system characterized by T-cell activation, increased regulatory control of IL-17 producing effector T cells and CD20 + T cells, and reduced control of B cells, which increase the risk of autoimmune events[21,22]. On the other hand,

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studies have shown that autoimmunity arises in patients with greater T-cell apoptosis and cell cycling in response to alemtuzumab-induced lymphocyte depletion, a phenomenon that is driven by higher levels of IL-21[23,24]. Secondary thyroid ADs are the most common type of AD that occurs after treatment with ALE. Thyroid disorders have been reported in approximately one-third of patients with no previous history of thyroid dysfunction, with most studies reporting a prevalence between 30 and 45%[25–29]. Thyroid AD mostly develops within 5 years after ALE infusion, with a peak incidence in the third year from the first course[27,30]. Other secondary ADs, such as immune thrombocytopenic purpura (1–3%)[31,32], glomerulonephritis[33,34]and haemolytic anaemia[35,36], have also been rarely reported after ALE infusions.

CLA safety data have shown that CLA is not associated with immune-mediated diseases[37]. In contrast to ALE and AHSCT, ADs have not yet been reported after CLA tablets, except for one case of glomerulonephritis, which occurred shortly after the fourth CLA treatment course[38]. IRT is a relatively novel therapy for MS, and it is currently unclear with some therapies whether the development of new ADs is therapy specific, or time-limited or whether specific ADs develop at predictable intervals after therapy exposure. In our study, we provided the follow-up data of patients with MS treated with IRT, with the aim of determining the proportion of patents who develop new ADs and to describe the nature of those ADs and the time to onset.

Results

A total of 179 patients with MS treated with IRT were included in the study. All patients had RMS. Thirty-seven patients (20.7%) were treated with AHSCT, 19 patients (10.6%) were treated with ALE infusions, and 123 patients (68.7%) were treated with CLA tablets. Patient disease characteristics and details for the patients by number of ALE or CLA courses are shown in Table 1. The mean duration of follow-up in patients treated with AHSCT was 53.6 ± 27.5 months, that in patients treated with ALE was 61.1 ± 20.1 months, and that in patients treated with CLA was 31.6 ± 13.3 months.

New autoimmune diseases were diagnosed in 16 patients (8.9%) during follow-up, with 11 (6.1%) females and 5 (2.8%) males affected: in 6 patients (16.2%) after AHSCT, in 8 patients (42.1%) after ALE and in 2 patients (1.6%) after CLA treatment (Table 2). The majority of ADs after IRT were of thyroid origin (n = 13, 81.3%), of which hyperthyroidism was the most common phenotype (n = 8, 50.0%). The vast majority of patients (63.5%) who presented with a thyroid event were diagnosed after ALE infusions. Significant thyroid eye disease requiring operative intervention was diagnosed in one patient (female, 42 years old). No thyroid dysfunction was diagnosed after CLA tablets were given. One patient (2.7%) with autoimmune thrombocytopenia was diagnosed after AHSCT.

The rates of ADs development did not differ between the sexes ($Chi^2 = 0.957$, $p > 0.05$), and age and treatment duration had no effect on AD frequency ($p > 0.05$). Patients with AD had a shorter disease duration than patients without AD did: 6.1 ± 3.5 years vs. 8.1 ± 6.0 years ($p = 0.032$).

The proportions of patients with secondary ADs (in black) among the total number of patients (in grey) for whom follow-up data are available per year after treatment with AHSCT, ALE and CLA are shown in Fig. 1, Fig. 2 and Fig. 3, respectively. The mean time to AD was 26.9 ± 13.9 months from initial treatment (range, 4–48 months). The shortest time to AD was in female patients who developed autoimmune thrombocytopenia at month 4 after AHSCT. The longest time to AD was 48 months in another female who developed hyperthyroidism after AHSCT. AD's were more common between 37 and 60 months after AHSCT (with the exception of one thrombocytopenia patient), more frequent between 12 and 36 months after ALE and more common in the first

	AHSCT (N-37)	ALE (N-19)	CLA (N-123)	Test
Single course Two courses	-	0 19 (100%)	7 (5.7%) 116 (94.3%)	-
Age	38.03 ± 5.8	35.7 ± 8.2	38.6 ± 11.9	ANOVA F = 0.596, p = 0.552
Female, N (%)	26 (70.3)	13 (68.4)	83 (67.5)	$\chi 2 = 0.950$ p > 0.05
Disease duration	8.8 ± 4.9	8.2 ± 5.5	7.6 ± 6.1	ANOVA F = 0.640, p = 0.528
Number of past DMT's, median (IQR)	2 (2–3.5)	2 (2–3)	1 (1–2)	CLA < ALE < AHSCT F = 32.5, p < 0.001**
Last known DMT • High efficacy therapies, N (%) • Platform therapies, N (%)	36 (97.3%) 1 (2.7%)	12 (63.1%) 7 (36.8%)	11 (8.9%) 107 (87.0%)*	CLA < ALE < AHSCT p < 0.001**
EDSS before treatment	5.6 ± 0.7	4.6 ± 1.1	3.4 ± 1.1	CLA < ALE < AHSCT ANOVA F = 67.4, p < 0.001
Number of relapses before treatment, median (IQR)	2 (2–3.5)	2 (2–3)	1 (1–2)	CLA < ALE < AHSCT F = 45.7, p < 0.001**

Table 1. Demographic and clinical characteristics of patients treated with IRT. AHSCT – autologous haematopoietic stem cell transplantation, ALE – alemtuzumab, CLA – cladribine, EDSS—Expanded Disability Status Scale, DMT's – disease modifying therapies. *in 5 patients CLA was started de novo. **Kruskal–Wallis test was used. ***p value is Fisher exact test.

Patient no	Gender	Age	Treatment	Follow-up, mth	Autoimmune diseases	Month*	AD severity level	Treatment of autoimmune disease	Outcome
1	F	30	AHSCT	85	Autoimmune thyroid disorder, hypothyroidism	44	Grade 2	Thyroid hormone alone	Remission after treatment
2	F	42	AHSCT	65	Autoimmune thyroid disorder, hyperthyroidism	18	Grade 3	Antithyroid drug, steroids, surgery (total thyroidectomy)	Remission after surgery
3	F	35	AHSCT	63	Thrombocytopenia	4	Grade 3	Steroids, IVIG, eltrombopag	Remission after eltrombopag
4	M	31	AHSCT	59	Autoimmune thyroid disorder, hyperthyroidism	45	Grade 2	Antithyroid drug alone	Remission after treatment
5	F	40	AHSCT	55	Autoimmune thyroid disorder, hyperthyroidism	48	Grade 2	Antithyroid drug alone	Remission after treatment
6	M	42	AHSCT	50	Autoimmune thyroid disorder, mild hypothyroidism	36	Grade 1	No therapy	Spontaneous resolution
7	F	31	ALE	90	Autoimmune thyroid disorder, hyperthyroidism	36	Grade 2	Antithyroid drug alone	Remission after treatment
8	F	41	ALE	80	Autoimmune thyroid disorder, mild hypothyroidism	40	Grade 1	No therapy	Spontaneous resolution
9	M	59	ALE	72	Autoimmune thyroid disorder, hypothyroidism	26	Grade 2	Thyroid hormone alone	Remission after treatment
10	F	31	ALE	68	Autoimmune thyroid disorder, hyperthyroidism	28	Grade 2	Antithyroid drug alone	Remission after treatment
11	F	35	ALE	65	Autoimmune thyroid disorder, hypothyroidism	19	Grade 2	Thyroid hormone alone	Remission after treatment
12	F	34	ALE	65	Autoimmune thyroid disorder, hyperthyroidism	17	Grade 2	Antithyroid drug alone	Remission after treatment
13	F	28	ALE	58	Autoimmune thyroid disorder, hyperthyroidism	33	Grade 2	Antithyroid drug alone	Remission after treatment
14	M	36	ALE	35	Autoimmune thyroid disorder, hyperthyroidism	13	Grade 2	Antithyroid drug alone	Remission after treatment
15	F	45	CLA	52	Psoriasis	10	Grade 2	Topical therapy	Only symptoms improved
16	M	27	CLA	36	Vitiligo	13	Grade 1	No therapy	No changes

Table 2. New autoimmune disorders after immune reconstitution therapy in MS patients. Mth – month, F – female, M – male, AHSCT – autologous haematopoietic stem cell transplantation, ALE – alemtuzumab, CLA – cladribine, IVIG – intravenous immunoglobulin. *month when AD was diagnosed after IRT.

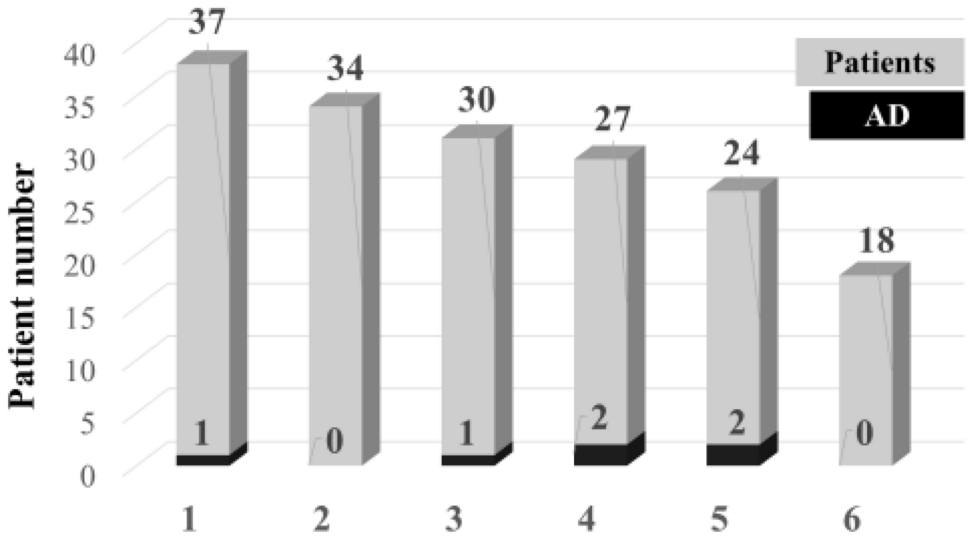

Fig. 1. Occurrence of secondary AD per year of follow-up in MS patients treated with AHSCT. 1,—up to 12 months; 2,—13 −24 months; 3,—25–36 months; 4,—37–48 months; 5,—49–60 months; 6,—> 60 months. AD,—autoimmune disorder; AHSCT,—autologous haematopoietic stem cell transplantation. The number of patients with AD is shown in black relative to the total number of treated patients in grey.

24 months after CLA treatment. No patients with ADs were identified after 60 months, although only 34 patients (19.0%) had longer follow-up.

Discussion

Here, we report our single-centre experience of autoimmunity with 179 MS patients treated with IRT. We included patients treated with IRT who had more immune system depletion effects and no continuous immunosuppression effects. This is the first study describing the development of secondary autoimmune complications after all IRT in MS patients and comparing the differences between them.

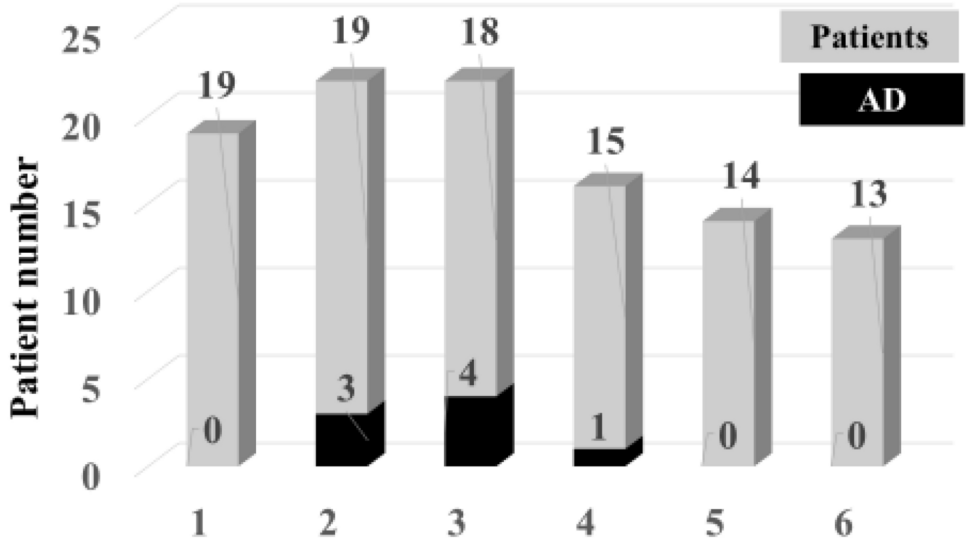

Fig. 2. Occurrence of secondary AD per year of follow-up in MS patients treated with ALE. 1,—up to 12 months; 2,—13 −24 months; 3,—25–36 months; 4,—37–48 months; 5,—49–60 months; 6,—> 60 months. AD,—autoimmune disorder; ALE,—alemtuzumab. The number of patients with AD is shown in black relative to the total number of treated patients in grey.

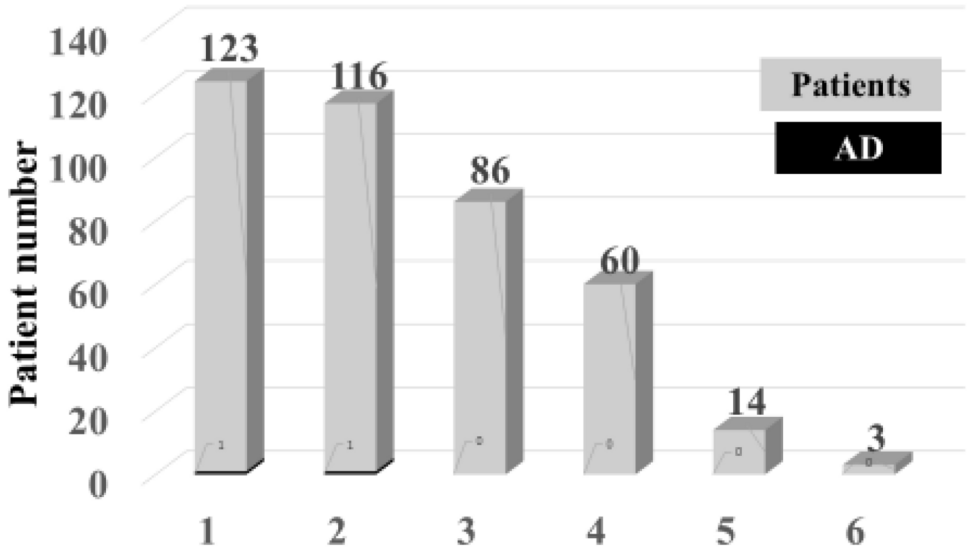

Fig. 3. Occurrence of secondary AD per year of follow-up in MS patients treated with CLA. 1,—up to 12 months; 2,—13–24 months; 3,—25–36 months; 4,—37–48 months; 5,—49–60 months; 6,—> 60 months. AD,—autoimmune disorder; CLA,—cladribine. The number of patients with AD is shown in black relative to the total number of treated patients in grey.

First, demographic and disease characteristics (age, sex and disease duration) did not differ among the three groups in our study; however, the disease activity characteristic of the groups were different: relapse rate, disability level, and increased activity were observed in patients treated with AHSCT, whereas the lowest activity was observed in patients treated with CLA tablets. Additionally, more patients with higher efficacy of DMT were in the ALE and AHSCT groups. In most countries, CLA tablets are considered a reasonable option for first- or second-line therapy in patients with MS, whereas ALE and AHSCT are generally reserved for patients who respond poorly to second-line therapy[39–42]. Patients with higher disease activity were treated with higher-efficacy DMT, as confirmed by our results.

The greater number of patients who developed ADs after IRT were patients treated with ALE. The majority of ADs that developed after IRT were of thyroid origin, mostly after ALE infusion. AD outcomes in the ALE group are comparable with previous results from multicentre studies in Europe and smaller datasets[10,11,25–28]. The occurrence of thyroid dysfunction after the second course of ALE (41% of patients) was the same as that reported

in previous studies[25,26,28,43,44]. In our cohort, the median follow-up in the ALE group was 61.1 ± 20.1 months, which was slightly greater than that reported in most previous studies[25,26,29]. Therefore, we reported the same occurrence of ADs with longer follow-up. Additionally, the highest rate of ADs in our study was observed during the second and third years after ALE infusions, so longer follow-up does not predict a higher incidence of ADs. For these reasons, 48-month clinical and biological monitoring is recommended after the last ALE infusion[45].

New ADs were diagnosed in 16.2% of patients from week 4 up to 5 years after AHSCT in our study. The previously published occurrence of posttransplant autoimmune diseases ranges from 10% to 20 – 23%[18,19,46,47]. Several theories have proposed concerning the different rates of autoimmunity after AHSCT. The main focus in recent years has been on the different types of conditioning regimens used before AHSCT. The increased risk of autoimmune disease development was increased by the use of ALE instead of anti-thymocyte globulin (ATG) in the conditioning regimen[19,46–48]. ATG was used in our patients, but the occurrence of AD after AHSCT was relatively high. The lower number of patients could have had an impact on the relatively greater occurrence of AD after transplantation. All autoimmune thyroid disorders in the posttransplant patients in our study were diagnosed later than they were diagnosed after ALE infusions, possibly because de novo development of T cell can be delayed up to several years after T-cell depletion during AHSCT, and secondary AD can be diagnosed later through follow-up[18,49].

The lowest occurrence of ADs in our study was associated with CLA treatment. These data are comparable to world data[37]; only one case of autoimmune glomerulonephritis was published after CLA treatment[38]. In our cohort, two new autoimmune diseases, vitiligo and psoriasis, were diagnosed after CLA in the early follow-up. Our cases are the first to show new autoimmune disease development after the administration of CLA tablets. The time of occurrence of AD in our CLA patients was also quite early: the first signs of the disease appeared at months 10 and 13 after the first CLA course. The lower occurrence of ADs after CLA than after ALE and AHSCT are likely due to the different immune reconstitution effect intensities. CLA is thought to deplete primarily memory B cells and effector T cells, but it spares naive T cells and long-lived memory T cells to a greater degree than ALE does[11]. On the other hand, the depletion of lymphocytes is more profound, and the repletion of T- cells is slower after ALE than after CLA[1].

The most common AD after IRT in our study was thyroid disorder, mostly after ALE and AHSCT, and the rates of AD did not differ based by sex or age among our patients. Although older age and female sex are known risk factors for autoimmune thyroid disease in general population studies[50], they were not associated with the development of AD in our study. The same results in terms of age and sex after IRT were also published by Cossburn et al.[29]; however, autoimmunity was assessed only after ALE. Our results and those of previous studies support the hypothesis that the mechanism by which autoimmune thyroid disorder occurs after ALE and AHSCT differs from that in the general population.

This study has several limitations, as we included fewer patients treated with ALE and AHSCT than with CLA; however, the follow-up was shorter in CLA patients than in ALE and AHSCT patients. The lower number of patients and the shorter follow-up period could have biased the study results. Additionally, it was descriptive single-centre study with no possibility of comparing the rate of occurrence of autoimmunity between different treatments. Furthermore, cladribine-treated patients had significantly lower disability rates and fewer previously used disease-modifying drugs, which might be another confounder. A greater number of drugs used in the past has a greater impact on the immune system and increases the likelihood of potential side effects. The key strength of our study lies in the fact that it is based on real-world clinical data prospectively collected by the same medical team at the same academic hospital centre, with criteria and goals for treatment remaining constant throughout the entire study period.

Methods

A single-centre retrospective noninterventional case series study using real-world data was conducted at Vilnius University Hospital Santaros Klinikos (VUHSK), Lithuania. The Lithuanian Bioethics Committee approved the study in 2011 (2011–01–27 Nr: L-12–01/2), the permission to continue the study was granted by the Lithuanian Bioethics Committee in 2018 (2018–02–22 Nr: 6B-18–41). A total of 179 MS patients treated with immune reconstitution therapy (AHSCT, ALE or CLA) between 2014 and 2023 were enrolled in the study. All methods were performed in accordance with the relevant guidelines and regulations. All patients signed the informed consent form for the collection of data and its use for research purposes.

Data were systematically acquired from electronic patient records. Patients' electronic health records were reviewed through a nationwide system that includes all patients' visits in all health care settings. Immune reconstitution treatment decisions were based on the clinical and radiological judgement of the neurology team at VUHSK. Patients were treated with two annual courses of ALE or CLA[3,4]. A medium-intensity conditioning regimen with cyclophosphamide and antithymocyte globulin was used for all transplant patients. Owing to the routine monitoring requirements, follow-up visits in ALE patients were performed every month five years from the first infusion and then every three months. Patients after the CLA course were monitored monthly three months after the treatment course and every three month after that. Patients after AHSCT were monitored monthly six months after the treatment and every three months thereafter.

The primary outcome measure of the study was the proportion of patients who developed new ADs. New AD was recognized to be caused by IRT in those cases when it was not present in the patient prior to therapy exposure. ADs were diagnosed on the basis of symptoms, medical history, blood tests, and,in some cases, imaging tests and biopsies. The diagnoses of all thyroid autoimmune diseases were confirmed by an endocrinologist upon endocrinological assessment, cytopenia was confirmed by a hematologist, and skin diseases were confirmed by a dermatologist upon dermatological assessments. The timing of an AD was defined as the day of first symptom manifestation or when the disorder was first recognized by a health care professional.

Statistical methods

The data were analysed via the statistical software package SPSS (version 23.0 for Windows). Continuous variables are reported as medians and ranges or means and standard deviations, whereas categorical variables are reported as absolute numbers and percentages of total patients. Kruskal–Wallis test was used to determine the differences between the means of the three treatment groups. Categorical variables were analysed via the chi-square test or Fisher's exact test. To check the normality of the distribution of quantitative variables, the Shapiro–Wilk test was used. A significance level of $p < 0.05$ was considered to indicate statistical significance.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

N.G. Conception and design of the study, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript. R.K. Concept of the study, revision of the manuscript for scientific accuracy. G.K. Overall revision for accuracy of the data, tables and figures, scientific accuracy of the manuscript. All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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