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Research article

# Alemtuzumab infusion-associated reactions and laboratory changes in patients with relapsing-remitting multiple sclerosis at baseline and first-year follow-up

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ABSTRACT

*Background:* Alemtuzumab (ATZ) is an anti-CD52 humanized monoclonal antibody indicated for treating highly active relapsing-remitting MS (RRMS). It alters the regulation of the immune system by depleting circulating lymphocytes. Changes in blood cell count, infusion-related reactions, and changes in vital parameters can be seen in the early period with ATZ.

*Aim:* Changes in blood tests, serum tests, vital parameters, and characteristics of infusion-associated reactions (IARs) observed during the first course of ATZ treatment and thereafter were evaluated.

*Materials and methods:* The systolic blood pressure (SBP), diastolic blood pressure (DBP), fever, heart rate (HR), changes in blood and serum tests, and IARs developed after the first course of 23 patients with RRMS who received ATZ treatment were evaluated by comparing the results of 26 patients with RRMS who received only intravenous methylprednisolone.

*Results:* Mean age was 36.60 ± 8.98, 73.9% female (n = 17), diagnosis time was 8.52 ± 3.64 years, pre-EDSS: 3.93 ± 1.80. No significant difference was found in vital parameters except for sub-febrile fever that developed on the first day. The number of white blood cells increased significantly after the first day. The hemoglobin level did not change. Lymphocyte (very high) and platelet (mild) counts decreased starting from the first days, and eosinophil (very high) and monocyte (moderate) counts decreased from the third day. There were no significant changes in liver enzymes, thyroid function tests, serum urea, creatinine, and lipid profile during 1-year follow-up. The IAR rate was 95.6% and occurred most frequently on the second and third days. The most common are dermatological findings (52%), headache (20%), pain (10%) and fatigue (8%).

*Conclusion:* Alemtuzumab has no appreciable effect on vital parameters during infusion. However, these changes are not clinically correlated, even if there is. Headache in the first days, dermatological (most common) findings, pain, and fatigue are seen in the following days. Most IARs can be resolved with symptomatic treatment and close follow-up. Lymphocytes, eosinophils, and monocytes are significantly reduced and return to baseline levels towards the end of the first year. The first year does not cause significant pathologies in other serum parameters. However, after the first year, watch out for associated autoimmune pathologies, especially thyroid involvement.

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## 1. Introduction

Alemtuzumab is an anti-CD52 humanized monoclonal antibody indicated for treating highly active relapsing-remitting MS (RRMS). CD52 is a surface antigen highly expressed in lymphocytes, monocytes, eosinophils, and natural killer cells, less expressed in neutrophils, and not expressed in platelets. ATZ reduces both T and B cells through the mechanism of complement and antibody-dependent cytolysis. After the first treatment cycle, almost all T and B lymphocytes are depleted, and repopulation begins a few weeks later. Returning to the initial level takes up to 1 year [1]. Monocyte and eosinophil counts decrease. Non-immune thrombocytopenia may occur in the acute phase after infusion [1]. It is usually asymptomatic and returns to normal within two months [2]. Changes in vital parameters can be seen after the infusion. Only results in systolic blood pressure, increase in systolic and diastolic blood pressure, or no change were reported [3–6]. There may also be a slight but insignificant increase in heart rate [7]. There is a high probability of an infusion reaction. The most common ones are urticaria or rash, headache, and fever. It is more common in the first cycle of Alemtuzumab and less likely in the second year and other subsequent cycles. Most IARs are mild or moderate. On the other hand, most serious IARs occur during the first infusion [8,9]. Notably, 39% did not require extra intervention, examination, prolonged hospitalization, or re-hospitalization [10]. This study aims to reveal the changes in vital signs, side effects, and blood cell changes observed in the acute period with ATZ infusion.

## 2. Materials and methods

### 2.1. Study design & population

The records of 23 patients who received Alemtuzumab treatment with the diagnosis of RRMS in our center between 01.01.2017 and 23.11.2023 were reviewed retrospectively. Ethics committee approval was received for the study (Approval no: 2023-7/27). All patients received routine alemtuzumab premedication. Blood cell counts, liver enzymes, thyroid function tests, serum urea, creatinine, and lipid profile were recorded immediately before infusion, on days three and five of infusion, and at one, six, nine, and twelve months post-infusion. Daily vital signs (blood pressure, fever, and heart rate) and side effects were recorded during the infusion. All patients included in the study were patients with RRMS who showed high disease activity and were resistant to other disease-modifying therapy (DMT). The previous DMTs were ocrelizumab, fingolimod, and natalizumab, in order of frequency.

IARs, neurological examinations, and vital changes during infusion were evaluated by three different neurologists, and all laboratory results were evaluated by a neurologist and an internal medicine specialist (who was also in the last year of the endocrinology fellowship program).

### 2.2. Premedication and infusion protocol

#### 2.2.1. Premedication

1 In the first three days, 1000 mg intravenous methylprednisolone (IVMP) was administered in 100 ccs 0.9% isotonic sodium chloride (NaCL) over 1.5 h.
2 Starting from day 1, Acyclovir peroral 200 mg 2x1 (continued for one month)
3 Pheniramine 27.5 mg (5 days)
4 Metoclopramide 10 mg IV (5 days)

#### 2.2.2. Infusion

Alemtuzumab 12 mg intravenous administered in 6–8 h, followed by 100 cc NaCL in 30 min.

### 2.3. Exclusion criteria

Patients with additional medication or other diseases affecting blood cell counts and serum tests were excluded. If the patient had more than one test, the averages were taken.

### 2.4. Statistical analysis

The Shapiro-Wilk test was used to examine whether the data showed normal distribution. Descriptive statistics are expressed as mean, standard deviation, or median (minimum-maximum) for quantitative data and frequency and percentage for qualitative data. T-test was used to compare two independent groups for normally distributed data, and Mann Whitney *U* test was used for data that did not show normal distribution. Repeated measurements were compared between groups by calculating the percent change value (percent change=(last measurement – first measurement)/first measurement) compared to the initial measurement. The Friedman test was used for in-group comparison of time-dependent repeated measures. Pearson Chi-square, Fisher-Freeman-Halton, and Fisher's Exact Chi-square tests were used to analyze categorical data. Bonferroni test, one of the multiple comparison tests, was used if statistical test results were significant. The relationships between the variables were examined with the Spearman correlation coefficient. The significance level was determined as $\alpha = 0.05$. Statistical analysis of the data was performed in the statistical package program IBM

SPSS 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

## 3. Results

### 3.1. Demographic data and clinical characteristics

The mean age was 36.60 ± 8.98 years, with 17 women and 6 men. The mean duration of the disease was 8.52 (1–14) years, and the annual attack rate before the start of treatment was 0.7 (0.27–3). The median follow-up period was 10.33 (7.2–65.9), with a total of 517 months. When ATZ was started, the mean EDSS (Expanded Disability Status Scale) was 3.93 ± 1.80. ATZ was switched from ocrelizumab(n = 12), natalizumab (n = 6) and fingolimod (n = 5) treatments, respectively. ATZ and the control group (IVMP) have a similar distribution in terms of gender and age. There was no difference in correlation analysis according to age, gender, and EDSS.

### 3.2. Changes in vital signs

No significant differences were found when SBP, DBP, and HR were compared daily before, during, and after infusion (Table 1). The fever on the first day was slightly higher than the control group. However, all of these moderate elevations observed during the infusion were sub-febrile, and none of the patients had a fever >38.2, requiring intervention. In addition, no increased risk was detected for the development of systolic or diastolic hypertension/hypotension or tachycardia/bradycardia that may require intervention (Fig. 1).

### 3.3. Infusion associated reactions and side effects

A total of 117 IARs developed in 22 of 23 patients (95.6%) during the first infusion. The most common were urticaria or rash, headache, myalgia, and fatigue. IARs were most common during or after the second and third infusion on that day (24% for both) (Fig. 2). Only one patient had severe diffuse urticaria and chest pain that required interruption or complete cessation of the infusion. While medical intervention was required in 38 (35.5%) of 117 reactions, only observation or slowing of the infusion rate was sufficient in the others.

In the following period, one of the patients who developed infection developed uncomplicated shingles caused by varicella-zoster virus. Twenty-three patients did not develop any drug-related autoimmune pathology in the first year follow-up (Table 2). One patient developed drug-related autoimmune kidney pathology in the 2 nd year, and 3 of the 5 patients who completed the 5-year follow-up period developed drug-related autoimmune thyroid pathology in the second and third years.

When the first alemtuzumab treatment was started, there was one patient diagnosed with hyperlipidemia and one patient with hypothyroidism who were under control with the treatment. 3 patients were in inactive HBsAg carrier state and were receiving antiviral treatment (tenofovir) before the infusion and during the follow-up period. In terms of both chronic diseases and comorbidities, no increase in existing pathologies or a new pathology (such as autoimmune thyroiditis, hepatitis or neoplasia) was observed after ATZ infusion.

### 3.4. Changes in blood cell count

There was no change in hemoglobin level with the first infusion of ATZ. In the first days, there was leukocytosis due to increased neutrophils. Platelet and lymphocyte counts decreased significantly from the third day, and monocytes and eosinophil counts were significantly lower in the fifth-day measurements compared to the control group. These decrease rates were 96.7% and 98% on days 3

**Table 1**
Demographic data and vital signs during ATZ and IVMP infusions.

| | | ATZ | IVMP | P | | | ATZ | IVMP | P |
|---|---|---|---|---|---|---|---|---|---|
| Sex (Female) | | n = 17 (73.9%) | n = 16 (60%) | 0.368 | Age | | 36.60 ± 8.98 | 35.36 ± 9.81 | 0.648 |
| **SBP** | 1st day | 108,50 | 110,00 | 0.388 | **HR** | 1st day | 85,00 | 80,00 | 0.085 |
| | 2nd day | 106,50 | 112,50 | 0.090 | | 2nd day | 84,00 | 79,00 | 0.239 |
| | 3rd day | 111,00 | 115,00 | 0.328 | | 3rd day | 77,50 | 81,00 | 0.050 |
| | 4th day | 110,00 | 113,00 | 0.391 | | 4th day | 75,50 | 80,00 | 0.064 |
| | 5th day | 105,00 | 116,00 | 0.050 | | 5th day | 80,00 | 77,50 | 0.497 |
| | Post-inf | 107,50 | 117,50 | 0.217 | | Post-inf | 78,00 | 75,50 | 0.377 |
| | 1st day | | | | | 1st day | | | |
| **DBP** | 1st day | 70,00 | 70,00 | 0.962 | **Fever** | 1st day | 36,55 | 36,25 | **0.003** |
| | 2nd day | 65,00 | 70,00 | 0.218 | | 2nd day | 36,50 | 36,20 | 0.883 |
| | 3rd day | 70,00 | 70,00 | 0.915 | | 3rd day | 36,60 | 36,30 | 1.000 |
| | 4th day | 67,50 | 70,00 | 0.464 | | 4th day | 36,45 | 36,10 | 0.322 |
| | 5th day | 67,50 | 70,00 | 0.066 | | 5th day | 36,50 | 36,30 | 0.965 |
| | Post-inf | 70,00 | 70,00 | 0.478 | | Post-inf | 36,60 | 36,20 | 1.000 |
| | 1st day | | | | | 1st day | | | |

**SBP:** Systolic blood pressure (mm Hg), **DBP:** Diastolic blood pressure (mm Hg), **HR:** Heart Rate (/min), **Fever** (°C).

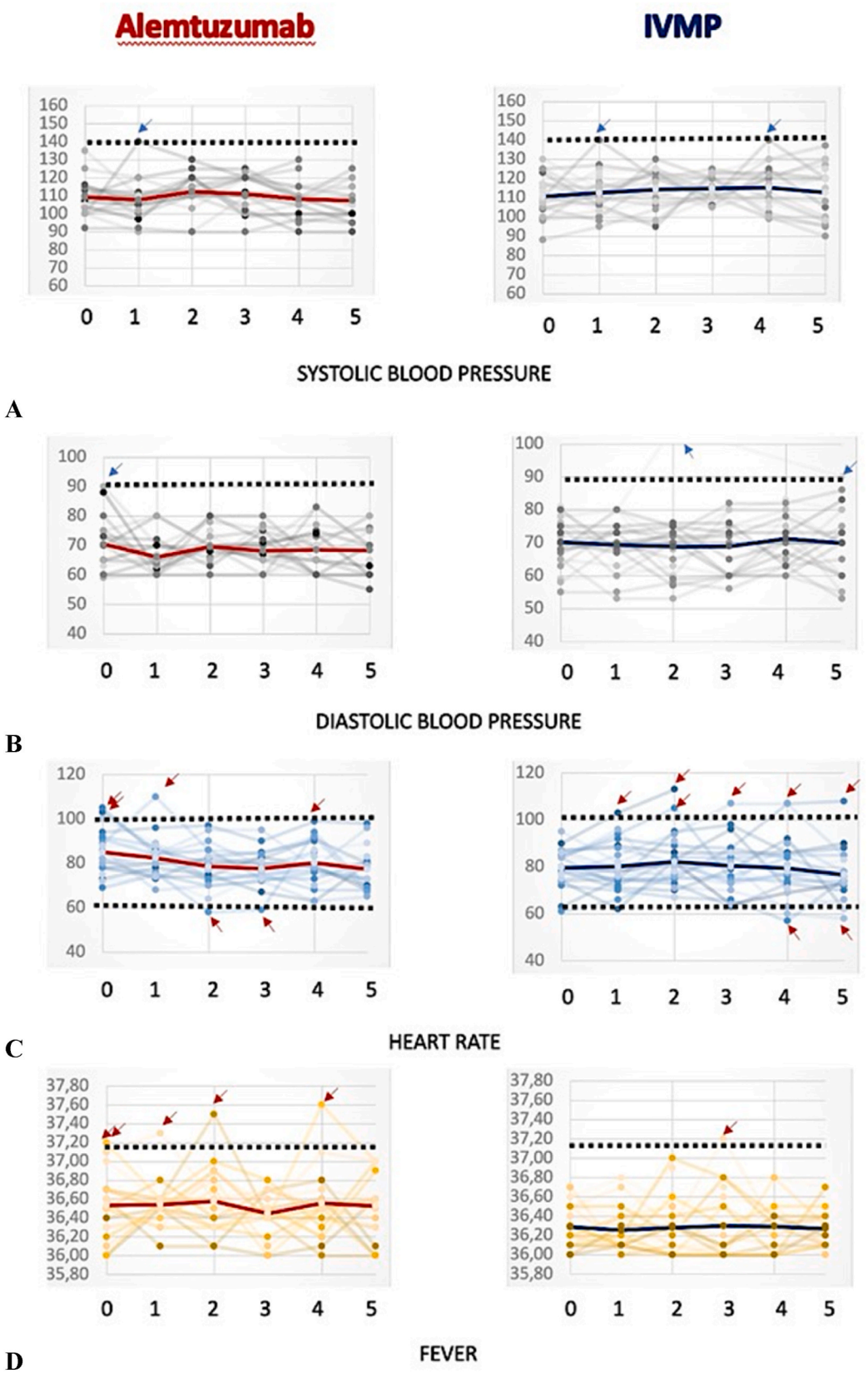


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**Fig. 1.** Changes in vital signs during alemtuzumab infusion.
**A:** Systolic blood pressure, **B:** Diastolic blood pressure, **C:** Heart rate **D:** Body temperature
Arrows; values that exceed the physiological range. 0 and 1 before starting ATZ therapy and within 12 h after finishing the first cycle dose. Baseline (0) and during infusion (1–5) days.

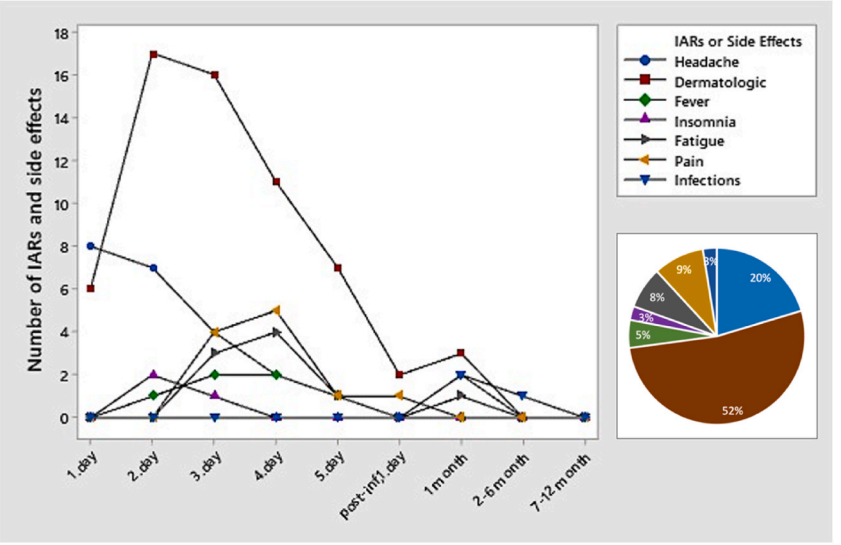


**Fig. 2.** Timings and rates of infusion associated reactions (IARs) or side effects.

**Table 2**
IARs and side effects during and after ATZ infusion (first year).

| Time | Total n (%) | Headache | Dermatologic | Fever | Insomnia | Fatigue | Pain | Infections | Autoimmune pathologies |
|---|---|---|---|---|---|---|---|---|---|
| | 117 (%) | 24 | 62 | 6 | 3 | 8 | 11 | 3 | – |
| **1st day** | 14 (12%) | 8 | 6 | | – | – | | – | – |
| **2nd day** | 28 (24%) | 7 | 17 | 2 | 2 | – | – | – | – |
| **3rd day** | 28 (24%) | 4 | 14 | 2 | 1 | 3 | 4 | – | – |
| **4th day** | 23 (20%) | 2 | 11 | 1 | – | 4 | 5 | – | – |
| **5th day** | 10 (9%) | 1 | 7 | – | – | 1 | 1 | – | – |
| **Post-inf. 1st day** | 3 (3%) | – | 2 | – | – | – | 1 | – | – |
| **1st month** | 8 (7%) | 2 | 3 | – | – | 1 | – | 2 | – |
| **2-6th month** | 1 (1%) | – | – | – | – | – | – | 1 | – |
| **7–12th month** | – | – | – | – | – | – | – | – | – |

and 5 for lymphocytes, 99.3% on day 5 for eosinophils, 80.4% on day 5 for monocytes, and 17.6% and 19.5% on days 3 and 5 for platelets compared to baseline (Table 3).

In the follow-up until the first year, lymphocyte, monocyte and eosinophil counts approached baseline levels at the end of the first year, platelet levels returned to baseline, and hemoglobin and leukocyte levels did not follow a similar course (Fig. 3).

**Table 3**
Blood cell count during and after infusion.

| | Days | ATZ | IVMP | P | | Days | ATZ | IVMP | P |
|---|---|---|---|---|---|---|---|---|---|
| **WBC** | 1st | 6760,00 | 8600,00 | **0.007** | **LYM** | 1st | 1570,00 | 1830,00 | 0.101 |
| | 3rd | 13230,00 | 12500,00 | **0.033** | | 3rd | 40,00 | 880,00 | **<0.001** |
| | 5th | 5830,00 | 10150,00 | 0.202 | | 5th | 30,00 | 1036,50 | **<0.001** |
| **HB** | 1st | 12,30 | 13,10 | 0.269 | **MON** | 1st | 475,00 | 512,00 | 0.726 |
| | 3rd | 11,90 | 13,20 | 0.305 | | 3rd | 172,00 | 149,00 | 0.762 |
| | 5th | 12,50 | 13,00 | 0.713 | | 5th | 57,00 | 203,00 | **0.006** |
| **PLT** | 1st | 226000,00 | 259000,00 | 0.180 | **EOS** | 1st | 127,00 | 70,00 | **0.045** |
| | 3rd | 167300,00 | 296000,00 | **<0.001** | | 3rd | 2,00 | 7,00 | 0.147 |
| | 5th | 181200,00 | 264500,00 | **<0.001** | | 5th | 1,00 | 10,00 | **0.006** |

**WBC:** White blood cells, **HB:** Hemoglobin, **PLT:** Platelets, **LYM:** Lymphocytes, **MON:** Monocytes, **EOS:** Eosinophils.

### 3.5. Changes in other serum tests

During the one-year follow-up period, AST and ALT were slightly elevated at the end of the first infusion, which could not be considered pathologic, but there was no significant change at the first month controls and thereafter (Fig. 4). There was no difference in serum urea, creatinine levels and pathologic change in aPTT. In the lipid profile evaluation, there was increase in HDL levels (%21) and decrease in LDL (%21), total cholesterol (%7) and triglyceride levels (%13.6) at the end of the first year compared to pre-drug (Fig. 5).

Except for the infusion period (first 6 days), when the changes in the mean or median values of all blood and serum parameters during the first year of follow-up were evaluated according to the proportion of patients with pathological values outside the reference range, only the lymphocyte decrease until the 9th month was significant (Table 4).

## 4. Discussion

To record a review of etiology after case series of disseminated cerebral hemorrhages with ATZ infusion. This was previously thought to be caused by an increase in mean daily blood pressure (SBP range from 15% to 55% with a peak range of up to 68%) [3]. A hypertensive hemorrhagic stroke resulting in death after infusion has been reported in the European Medicines Agency database. In

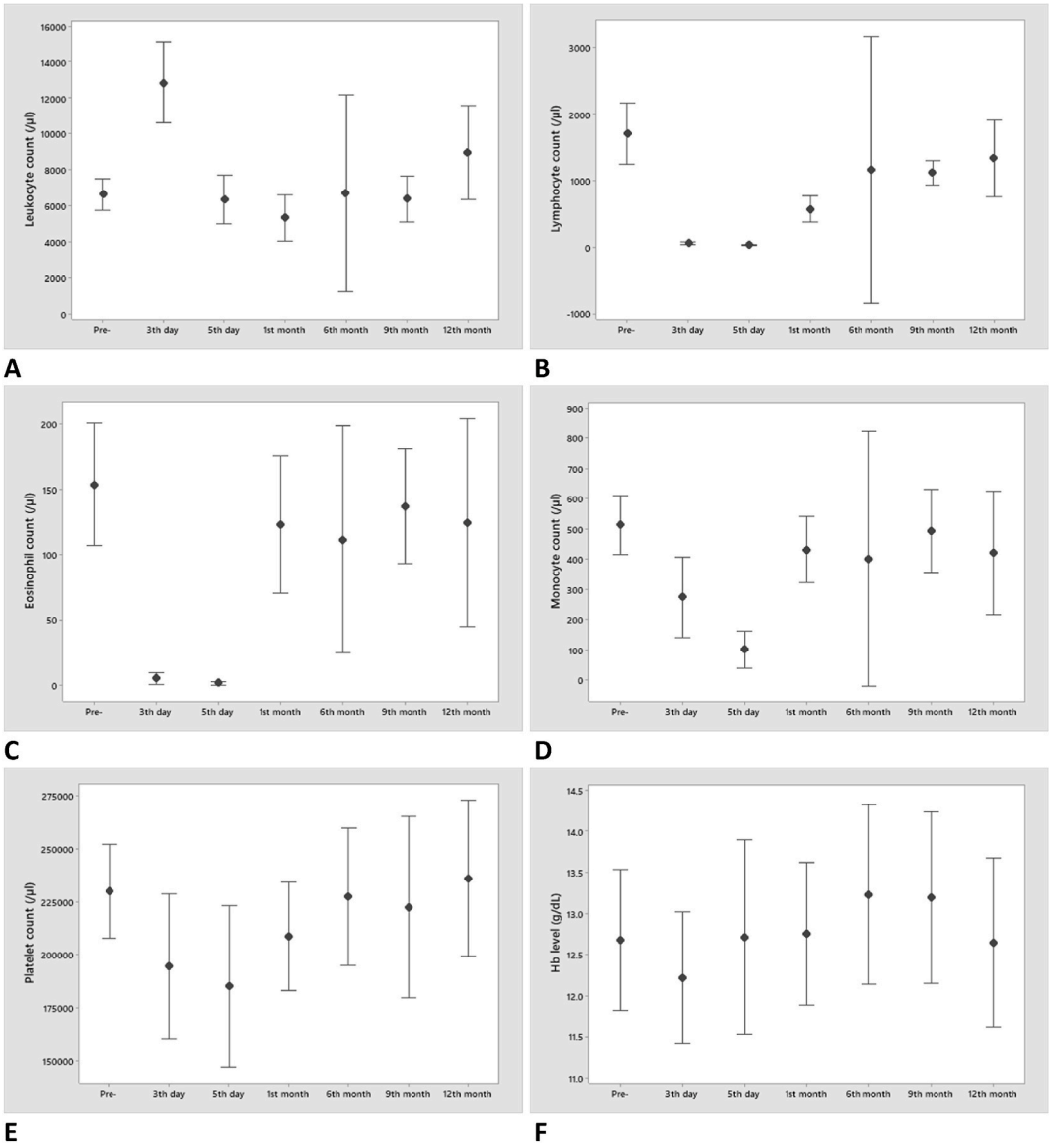


**Fig. 3.** Blood cell count changes during and within the first year after ATZ infusion treatment.
**A:** Leukocyte, **B:** Lymphocyte, **C:** Eosinophil, **D:** Monocyte, **E:** Platelet and **F:** Hemoglobin level.

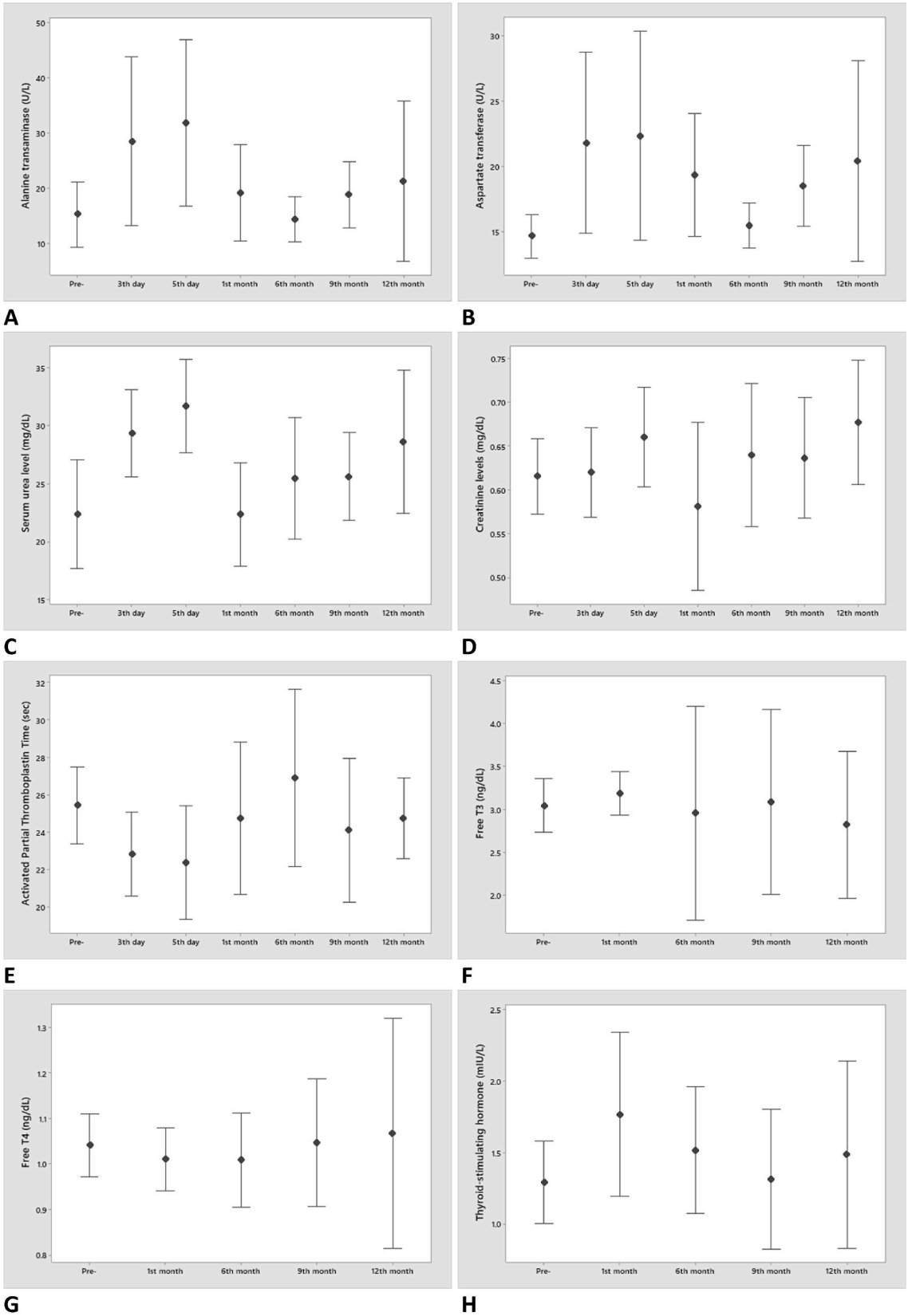


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**Fig. 4.** aPTT, liver enzymes, renal and thyroid function tests during and within the first year after ATZ infusion treatment.
**A:** Alanine transaminase, **B:** Aspartate transferase, **C:** Serum urea, **D:** Serum creatinine, **E:** Activated partial thromboplastine time **F:** Serum free triiodothyronine, G: Serum thyroxine, H: Serum thyroid-stimulating hormonelevels.

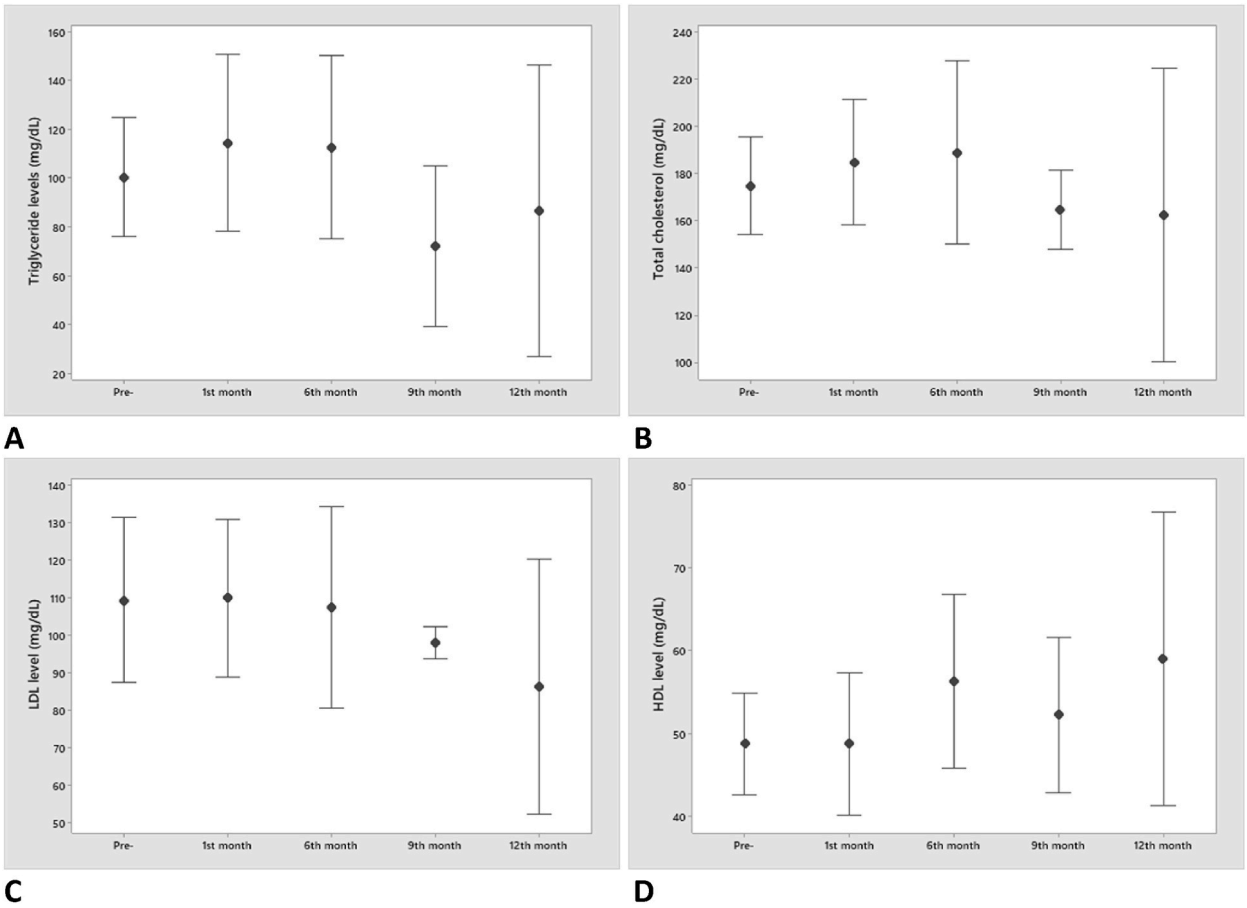


**Fig. 5.** Lipid profile changes during and within the first year after alemtuzumab infusion treatment.
**A:** Triglyceride, **B:** Total cholesterol, **C:** Low-density lipoprotein **D:** High-density lipoprotein.

addition to studies indicating increases in SBP and DBP during infusion, there are also studies in which only an increase in SBP or no change was observed [1,3,5,6]. Different results may be related to patient selection, various risk factors (age, body mass index, smoking, cardiovascular disorders, etc.), or different infusion or premedication (IVMP, etc.) administration protocols [4]. In a recent study questioning the change in vital parameters considering the premedication regimen (IVMP), an increase in SBP (12.8/8.1) and HR (82.5/73.2) with ATZ was reported [7]. The pathophysiological mechanism of ATZ-associated SBP increase is unclear. It is assumed that an increase in SBP develops as a reflection of the systemic inflammatory reaction infused due to the release of proinflammatory cytokines. Recently, it has been accepted that not only hemodynamic changes alone are the default mechanism for cerebral hemorrhages, but also endothelial or platelet dysfunction is responsible for this. Our study did not find a significant difference in vital parameters (blood pressure, fever, heart rate) with ATZ infusion compared to the control group receiving IVMP.

Alemtuzumab infusion-related reactions occur in approximately 84–94%. In CARE-MS I-II studies, it was reported that 90.1% [8,9]. The most common are dermatological findings (urticaria or rash), headache, and fever. It is more common in the first cycle of Alemtuzumab and less likely in the second year and other subsequent cycles. Most serious IARs occur during the first infusion. Notably, despite its high frequency, more than one-third of IRRs do not require any intervention, prolonged hospitalization, or re-hospitalization [11,12]. In CARE-MS I-II studies, most of them were mild to moderate, and 3.1% were reported to be severe (atrial fibrillation, hypotension, chest pain, tachycardia, nausea, headache, urticaria, and severe pyrexia) [8,9]. Anaphylaxis is rare, and other changes in vital signs during and after the infusion are usually clinically insignificant. Pre-IVMP implementation significantly reduces IRRs [13]. Most of the IARs formed in our study developed on days 2 and 3. Headache was more frequent in the first days, and dermatological findings, pain, and fatigue were more frequent in the following days. Only one patient did not react, and the incidence of IAR was 95.6%, higher than the literature. On the other hand, only one patient (4.4%) had a severe reaction that required

**Table 4**
Comparison of mean or median changes in all blood parameters at 1, 6–9 and 12 months compared to baseline, comparison of changes in the proportion of patients developing pathology compared to baseline.

| Months | Median or mean[a] | P Value | n(%)[b] | P Value | Median or mean[a] | P Value | n(%)[b] | P Value |
|---|---|---|---|---|---|---|---|---|
| | Lymphocyte (1090–2990)[c] | | | | Monocyte (240–790) | | | |
| 1 | **570** | **<0.001** | **17(89.5)** | **<0.001** | 430 | 0.37 | 2(10.5) | 0.268 |
| 6–9 | 1117 | 0.05 | **4(80)** | **0.016** | 492 | 0.3 | 2(10) | 0.748 |
| 12 | 1335 | 0.08 | 8(50) | 0.104 | 418 | 0.26 | 3(30) | 0.138 |
| | **Eosinophil (30–440)** | | | | **Platelet (155–366 x10$^3$)** | | | |
| 1 | 123 | 0.29 | 16(84.2) | 0.093 | 208.83 | 0.14 | 2(10.5) | 0.163 |
| 6–9 | 137 | 0.24 | 17(85) | 0.556 | 222.55 | 0.62 | 2(11.1) | 0.579 |
| 12 | 124 | 0.13 | 9(90) | 0.133 | 235.98 | 0.75 | 0 | 1 |
| | **Ast (5-34)** | | | | **Alt (8-55)** | | | |
| 1 | 19.3 | 0.09 | 1(6.3) | 0.333 | 19.13 | 0.61 | 1(6.7) | 0.334 |
| 6–9 | 18.5 | 0.28 | 1(5.3) | 0.331 | 18.77 | 0.47 | 1(5.6) | 0.331 |
| 12 | 20.4 | 0.08 | 1(10) | 0.343 | 21.2 | 0.21 | 1(10) | 0.343 |
| | **Urea (12.8–42.8)** | | | | **Creatinine (0.6–1.2)** | | | |
| 1 | 22.3 | 0.71 | 0 | 0.336 | 0.58 | 0.44 | 0 | 1 |
| 6–9 | 25.6 | 0.3 | 0 | 0.332 | 0.63 | 0.03 | 0 | 1 |
| 12 | 28.6 | 0.02 | 1(10) | 0.343 | 0.67 | 0.28 | 0 | 1 |
| | **HDL (<35)** | | | | **LDL (<130)** | | | |
| 1 | 48.7 | 0.9 | 2(15.4) | 0.165 | 109.8 | 0.26 | 2(16.7) | 0.341 |
| 6–9 | 52.2 | 0.32 | 1(7.1) | 0.584 | 97.8 | 0.27 | 1(7.1) | 1 |
| 12 | 59 | 0.68 | 0 | 1 | 86.2 | 0.5 | 0 | 1 |
| | **TG (<150)** | | | | **TK (<200)** | | | |
| 1 | 114.2 | 0.43 | 4(30.8) | 0.584 | 184.5 | 0.96 | 3(30) | 1.000 |
| 6–9 | 72.1 | 0.25 | 1(8.3) | 1.000 | 164.3 | 0.54 | 1(8.3) | 0.341 |
| 12 | 86.6 | 0.55 | 0 | 1 | 162.4 | 0.38 | 2(40) | 1.000 |
| | **aPTT (23–31.9)** | | | | **TSH (0.35–4.94)** | | | |
| 1 | 24.72 | 0.92 | 0 | 1 | 2.12 | 0.28 | 2(14.3) | 0.336 |
| 6–9 | 24.10 | 0.64 | 0 | 1 | **1.31** | **0.01** | 1(6.7) | 1.000 |
| 12 | 24.74 | 0.77 | 0 | 1 | 1.48 | 0.72 | 0 | 1 |
| | **Free T4 (0.7–1.48)** | | | | **Free T3 (1.71–3.71)** | | | |
| 1 | 1.01 | 0.34 | 1(8.3) | 0.341 | 3.18 | 0.91 | 0 | 0.391 |
| 6–9 | 1.00 | 0.65 | 0 | 1 | 3.09 | 1 | 0 | 1 |
| 12 | 1.06 | 0.57 | 1(12.5) | 0.363 | 2.82 | 0.34 | 0 | 0.500 |

[a] Median or mean values were taken depending on the normality of the distribution.
[b] Number of patients with pathological values; Those below the normal range for lymphocyte, monocyte, eosinophil, platelet and HDL, those above the normal range for ast, alt, urea, creatinine, LDL, TG, TC and aPTT, and those both above and below the normal range for TSH, free T4 and free T3.
[c] ; Normal reference ranges of our center.

interruption or discontinuation of the treatment. Like the literature, one-third of the patients did not require additional medical follow-up/treatment for IARs. One of the drawbacks of ATZ treatment is IARs. However, ATZ infusion-related reactions have decreased considerably with IVMP, antihistaminic and antipyretic treatments applied before. Therefore, the avoidance of patients or physicians has also decreased.

A neutrophil increase can be observed in the early post-infusion period due to cytokine release. However, CD52 surface antigen is expressed less on the surface of neutrophils than on other immune cells. As an effect of this, mild neutropenia can be detected after 4–6 weeks. Apart from these two conditions, neutropenia may also occur if a severe cytokine storm develops in the acute period. On the other hand, both T and B lymphocytes are almost entirely depleted after the first treatment cycle with complement and antibody-dependent cytolysis. Repopulation begins after a few weeks. B lymphocytes do not reach pre-infusion levels before six months, and T lymphocytes at 12 months. Non-immune thrombocytopenia may occur in the acute period after the infusion. The first case series found an average of 40% reduction in platelet count. However, this decrease did not reach the values where the bleeding risk increased. This reduction rate decreased after the premedication application. Furthermore, it was understood that this was usually asymptomatic and then returned to normal within two months [2,14]. Moderate thrombocytopenia in the early period is assumed to be associated with cytokine release, not autoimmunity. Long-term follow-up results revealed that thrombocytopenia was not observed except for immune thrombocytopenias. In our study, lymphocyte and thrombocyte counts decreased earlier. On the fifth day, lymphocyte and eosinophil counts were almost completely depleted, while monocyte counts decreased to one-fifth of the initial level. The platelet count decreased moderately by one-fifth. These changes in blood cells were not associated with complications (infection, thrombosis, bleeding, etc.). ATZ initiates cytolysis steps by interacting with CD52 surface antigens on cell surfaces. With this effect, profound changes are seen in the early period. As a result of cell destruction, both adverse reactions and changes in the number of cells may be affected by the release of some cytokines, chemokines, etc. However, as with IARs, these changes in cell numbers are not of grave concern. Close monitoring and follow-up are sufficient for these, and the patient's clinical condition is essential.

We did not find any studies in the literature on the effect of alemtuzumab treatment on lipid profile. We found positive changes in lipid profile (increase in HDL, decrease in LDL, total cholesteorol and triglyceride levels), which we could not show statistically significant. However, this is probably due to the effect of the diet (foods to avoid, such as raw or lightly cooked sprouts, seafood, beef, poultry, and lamb, lunch meats like cold cuts and chicken liver, unpasteurized or raw milk, ice cream, and cheese) we recommended at

the beginning and after treatment. Because of the risk of serious side effects such as listeria meningitis, patients are very careful about this issue.

## 5. Strenghts and limitations of the study

The fact that only five patients completed the entire ATZ course and follow-up period (five years) led us to restrict the aim of this study to serum tests, blood cell count changes and drug-related side effects at the first infusion and for the first one-year period in patients who started treatment. Monitoring of all patients continues, and we will also share our long-term (>5 years) safety and efficacy results in the future. The other of the main limitations of the study include the fact that we did not perform body mass index assessment and dietary habits questionnaire at each visit.

## 6. Conclusion

In general, we did not detect the effect of Alemtuzumab treatment on blood pressure, fever, and heart rate, although a few studies have reported a mild effect. Even if changes in these parameters exceed the physiological limits observed on a patient basis, this effect is small, does not constitute clinical seriousness, and can be easily managed. In IAR, headache is seen in the first days, and dermatological (most common) findings, pain, and fatigue are seen in the following days. Most IARs can be resolved with symptomatic treatment, close monitoring, or slowing the infusion rate.

Changes in blood cells in the early period: Lymphocyte (very high) and platelet (mild) counts decrease faster than eosinophil (very high) and monocyte (significant) counts (from the third day). Lymphocytes and eosinophils are almost entirely more depleted than others. However, there is no clinical correlation with these changes. Among other serum tests, we found no change in liver enzymes, renal function tests, coagulation factors and lipid profile. However, since the follow-up period of the patients after treatment is still short, our evaluations are valid for the first one-year period. In follow-ups longer than 1 year, we find the development of autoimmune thyroid pathology, especially in the 2 nd year, noteworthy. However, the follow-up of the patients continues for a definitive conclusion.

Changes in vital parameters, IARs, blood cell counts and routine serum tests during infusion and at follow-ups should not cause physicians to be concerned about ATZ infusion.

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## Disclosure statement

The authors report that there are no competing interests to declare.

## Ethical declaration

All procedures followed the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution.

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## CRediT authorship contribution statement

**Furkan Saridas:** Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Filiz Mercan Saridas:** Writing – original draft, Validation, Formal analysis, Data curation, Conceptualization. **Emine Rabia Koc:** Resources, Data curation. **Omer Faruk Turan:** Writing – review & editing, Supervision, Resources, Project administration.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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