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Marked increase of procalcitonin after the administration of anti-thymocyte globulin in patients before haematopoietic stem cell transplantation does not indicate sepsis: a prospective study

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Abstract

Introduction

Procalcitonin (PCT) and C-reactive protein (CRP) are established markers of infection in general population. In contrast, several studies reported falsely increased PCT levels in patients receiving T-cell antibodies. We evaluated the validity of these markers in patients scheduled for haemopoietic stem cell transplantation receiving anti-thymocyte globulin (ATG) during conditioning. We also assessed renal and liver functions and their relationship to PCT and CRP changes.

Methods

Twenty-six patients without clinical signs of infection were prospectively studied. ATG was administered in up to three doses over 5 days. PCT, CRP, white blood count (WBC), urea, creatinine, glomerular filtration rate (GFR), bilirubin, alanin amino-transferase (ALT) and gamma-glutamyl transferase (GGT) were assessed daily during ATG administration. Pharyngeal, nose and rectal swabs and urine samples were cultured twice weekly. Blood cultures were obtained if clinical symptoms of infection were present.

Results

Baseline (BL) levels of both PCT and CRP before ATG administration were normal. WBC count decreased after ATG administration ($p=0.005$). One day after ATG administration, both PCT and CRP levels increased significantly, returning to BL levels on day 4. Microbiological results were clinically unremarkable. There was no interrelationship between PCT levels and BL markers of renal or liver functions ($p>0.05$ for all comparisons). Bilirubin and GGT were increased on days 2-5 and ALT on day 3 ($p<0.05$ vs. BL). No difference in renal functions was observed. Three patients developed

bacterial infection on days 7-11 with different dynamics of PCT and CRP. There was no association between the number of ATG doses and PCT levels, or between the risk of developing infection and previous PCT levels.

Conclusion

ATG triggered a marked early surge in PCT and CRP followed by a steady decrease over 3 days. The dynamics of both PCT and CRP was similar and was not associated with infection. PCT levels were independent of renal and liver functions and were not predictive of further infectious complications. A direct effect of ATG on T lymphocytes could be the underlying mechanism. Hepatotoxic effect could be a contributing factor. Neither PCT nor CRP is a useful marker that can identify infection in patients receiving ATG.

Introduction

Patients undergoing allogeneic hematopoietic stem cell transplantation are subjected to substantial immunoalteration that puts them at increased risk for acquiring infection. Immunosuppression during conditioning phase before engrafting is induced by pharmacotherapy or total body irradiation. This results in significantly altered inflammatory response to infection. Clinical and laboratory markers of sepsis are of limited value. White blood count (WBC) is intentionally decreased and therefore has little information value. Fever, another important clinical sign, can be caused by multiple factors or, in contrast, can be absent. Biochemical markers of inflammation - C-reactive protein (CRP) and procalcitonin (PCT) – were shown to be able to reliably diagnose infection in general population. PCT seems to be superior in early detection of inflammation. It also enables to differentiate between systemic inflammatory response syndrome (SIRS) and sepsis.[1] PCT concentrations are increased even in immunocompromised septic patients.[2] In neutropenic patients, PCT helps to identify those who require antibiotic treatment.[3,4]

Anti-thymocyte globulin (ATG) is frequently used as a part of conditioning regimen in patients scheduled for allogeneic haematopoietic stem cell transplantation. In those patients, freedom from infection before engraftment is of utmost importance. ATG administration could be associated with systemic reaction, including fever and hypotension comparable to sepsis. The ATG-induced depletion of leukocytes makes one of the key diagnostic criteria of SIRS/sepsis[5] useless. Thus, biochemical markers of inflammation could be beneficial to differentiate between infectious vs. non-infectious complications in this specific population.

We prospectively evaluated the validity of CRP and PCT to diagnose infection in patients receiving ATG prior to haematopoietic stem cell transplantation. We also assessed renal and liver functions and their relationship to PCT and CRP changes.

Materials and Methods

We prospectively evaluated a cohort of twenty-six adult patients indicated for ATG conditioning regimen prior to haematopoietic stem cell transplantation in an observational non-randomized study. The patients were treated at Institute of Haematology and Blood Transfusion in Prague, Czech Republic. The study was approved by the Institutional Review Board. The purpose and procedures of the study were explained to participants, and a written informed consent was obtained.

Interventions:

Conditioning regimen was selected according to the underlying disease. ATG dose was selected according to donor-patient matching. A test dose of ATG (20 mg) was given after the baseline samples were obtained on day 0. Afterwards, ATG was administered once daily at a dose 20 mg/kg during 6 h infusion, in those patients who were indicated for total dose of 40 mg/kg, 20 mg/kg was administered the next day. Typically, there were two to three doses before transplantation.

Blood samples were drawn under aseptic conditions from a central venous catheter daily until transplantation. Heparinized plasma was used for PCT, CRP, renal and liver function tests. PCT was measured by enzyme-linked fluorescence immunoabsorbent assay (VIDAS BRAHMS PCT, bioMérieux). CRP was measured by turbidimetry (Modular SWA, Roche). WBC was analyzed from K_3 EDTA samples by a blood count analyser (Advia 120, Bayer). Turbidimetry (Modular SWA, Roche) was also

used for analysis of alanin amino transferase (ALT), gamma-glutamyl transferase (GGT) and bilirubin to assess liver function and urea, creatinine and glomerular filtration rate (GFR) to assess renal function.

Pharyngeal, nose and rectal swabs and urine samples were obtained prior to the initiation of the treatment, and twice weekly afterwards. Same samples plus blood cultures were obtained from all lumens of the central venous catheters and a peripheral vein when body temperature (measured in the axilla) increased above 37.5 °C. Blood cultures were cultivated for both aerobic and anaerobic bacteria, and fungi (bacT/ALERT, bioMérieux).

Statistical analysis

The plasma concentrations of biochemical markers are reported as mean values ± standard deviation (SD) unless marked otherwise. Given a non-parametric distribution of results, concentrations of markers were compared using the Kruskal-Wallis test. Correlations between levels of markers were examined with Spearman's rank correlation coefficient. PCT levels were analyzed and categorized into quartiles according to a concentration to evaluate their association with the post-ATG febrile/infectious complications. All statistical analyses were performed using Statistica CZ 8.0 software (Statsoft, USA). All tests were 2-tailed, and p values <0.05 were considered statistically significant.

Results

The demographic data and patients' characteristics are outlined in Table 1.

A significant increase in PCT was observed starting 24 h after ATG administration. The initial surge was followed by a slow, steady decrease. On Day 5, PCT levels were still increased, but there was no statistical difference vs. BL levels. The dynamics of CRP changes were similar to PCT, but CRP returned to BL values one day earlier. Similar statistically significant trends were observed for bilirubin and GGT. In contrast, ALT increased only transiently on day 2. There were no changes in urea, creatinine or GFR during conditioning. Progressive depletion of leukocytes was observed over time. (Figure 1)

There was no statistically significant interrelationship of PCT levels and markers of renal or liver functions ($p < 0.05$ for all comparisons). (Table 2)

The relative odds of post-ATG febrile complications did not increase significantly with each increasing quartile of baseline PCT concentration, such that patients in the highest versus lowest quartile did not have any increase in risk. After adjustment for CRP, the concentration of PCT remained unassociated with the risk of post-ATG febrile complications. (Table 3) There was no relationship between the number of ATG doses and PCT concentrations ($p=0.16$). (Figure 2)

Microbiological cultures of the pharyngeal, nose and rectal swabs and urine samples yielded clinically insignificant results. Blood cultures obtained during conditioning did not grow any bacteria or fungi over 7 day inoculation period.

Three patients developed sepsis 7-11 days after the ATG conditioning. The changes in PCT and CRP were different from those observed during conditioning. (Table 4)

Discussion

Both PCT and CRP have been shown to successfully diagnose systemic inflammation in various patient populations. A recent review of the role of PCT in febrile neutropenic patients suggested the superior role of PCT over other markers of infection in this population.

Patients undergoing conditioning before haematopoietic stem cell transplantation represent a distinct population with significantly altered immune response. This creates a challenging scenario for clinical diagnosis of incipient infection that could be potentially catastrophic if not discovered early. Conditioning with ATG, a heterogeneous protein, can be associated with adverse reactions, mainly circulatory instability and/or respiratory insufficiency. The severity of this reaction could be highly individual and in selected cases closely resemble sepsis. Ancillary biochemical tests that would readily detect infection would be of great benefit.

In our cohort of patients undergoing conditioning with ATG we observed a characteristic early surge in PCT and CRP, followed by a steady decline to a near-normalization on day 4. Yet, this was not associated with clinical infection, as monitored by microbiological cultures. Thus, neither PCT nor CRP proved useful as a valid complementary diagnostic tool at this setting.

Our observation has some support in the literature. Several previous reports suggested limited diagnostic value of PCT and CRP in the presence of anti-T lymphocyte antibodies. In kidney transplant patients receiving pan-T-cell antibodies, Sabat et al. found increased PCT concentrations that were comparable to those observed in sepsis. Similarly to our results, the early surge was observed 24 h after the initiation of the

treatment. The increase in TNF-α preceded the increase in PCT and was detectable as early as few minutes after ATG administration. However, those patients did not have any infection.[6] Similarly, Zazula et al. found increased PCT levels in orthotopic liver transplant recipients on the first day after surgery, with more marked increase in those who received ATG. PCT decreased independently of further ATG administration in both groups of patients. No evidence of infection was present in either group.[7]

Dornbusch et al. in a small retrospective study evaluated the diagnostic value of PCT and CRP in differentiating sepsis and febrile reaction after administration of anti-T-lymphocytes antibodies in pediatric patients. Neither PCT peak levels nor PCT concentrations 3 days after the onset of febrile reactions differed between septic patients and those receiving T-cell antibodies. Both PCT and CRP showed a trend similar to our observation, except for 5 out 21 patients whose CRP remained increased for 20 days irrespective of the duration of T-cell antibody administration.[8]

Pihusch et al. prospectively studied PCT, CRP and interleukin-6 (IL-6) in 350 stem cell recipients. Conditioning with ATG increased all monitored markers. In neutropenic patients receiving ATG there was no difference in PCT levels between patients with and without infections. After engraftment, PCT levels in patients without infections were significantly lower than in patients with infectious complications. However, the initial increase was less pronounced than in our cohort, but persisted longer.[9]

ATG is a mixture of antibodies against T cells with direct effect. The binding location of ATG on lymphocytes is mainly CD2, CD3, CD4/CD28, CD7+, LFA-1+ and

ICAM-1, receptors characteristic for T cells. The main mechanism of action is opsonisation and lysis by complement activation, leading to T-cell depletion.

The evidence suggests that the increase in PCT and CRP is not restricted to ATG. Similar reactions were observed after treatment with other T-cell antibodies, namely OKT-3. Treatment with monoclonal CD-52 antibody alemtuzumab triggered even higher levels of PCT and CRP, comparable with Gram-negative sepsis.[10]

The exact function, mechanism and the site of PCT production is yet to be fully unveiled. PCT activity has been identified in human leukocytes.[11] Others have suggested that liver,[12,13] lungs, neuroendocrine cells or various other tissues are possible production sites.[14,15]

Profound stimulatory effect of tumor necrosis factor (TNF-α) on PCT mRNA levels[11] or PCT itself was observed. After TNF-α administration, PCT reached half-maximal concentrations within 8 h -- 12 h earlier than CRP. It was suggested that PCT and acute phase proteins such as CRP are induced by similar pathways.[12] It could be hypothesized that the T-cell antibody induced increase of PCT is mediated via release of TNF-α and does not represent a direct effect of the antibody.[16]

In our study, induction of PCT increase by ATG administration can be explained mainly by lymphocytes destruction. However, the contribution of hepatotoxicity must also be considered. As the dynamics of PCT and CRP changes are similar, we do not believe that a difference in half-time of these parameters plays a role here.[17]

Bacterial infection with positive blood cultures developed in three patients in our study on days 7 to 11 after the last ATG dose. The dynamics of PCT and CRP changes in

those patients during this episode were different from the characteristic course of ATG-induced changes, and were not associated with actual WBC.

Understanding the mechanisms of PCT release could help to elucidate its increase in other non-infectious conditions, as described below. The extent of this increase in our cohort was not dependent on initial liver and renal functions or WBC. It was not predictive within the context of subsequent infectious complications and/or mortality. It could be speculated that the extent of PCT increase is related to a certain immunological body reserve that may not be fully reflected by actual WBC or, more specifically, transition of monocytes into macrophages.

A variety of clinical conditions with increased PCT of non-infectious causes were reported, including cardiac surgery,[18] and heatstroke.[19] In healthy term neonates, transient increase in PCT peaking at 24 h after birth and gradually decreasing over first 48 h of life was observed.[20] In chronic renal insufficiency patients, results are conflicting. In pediatric patients, a small increase in baseline PCT levels were observed.[21] Adult patients undergoing chronic hemodialysis treatment had normal PCT levels. In contrast, CRP was markedly increased in patients undergoing short- and long-term hemodialysis. PCT, but not CRP, was increased in patients on peritoneal dialysis.[22]

An isolated increase in PCT but not CRP or other inflammatory parameters were registered in patients with medullar thyroid carcinoma.[23,24]

Our study has limitations. We did not assess other markers that could be considered to augment the diagnosis of infection in neutropenic patients, as explored by others, e.g. IL-6, IL-8, TNF-α, endotoxin, serum amyloid A or neopterin.[25] Also, we did not study any patients that would acquire infection during ATG conditioning and

would represent a control group. This situation is extremely rare and only few cases were reported.[9] Based on our results and available literature, we are not able to recommend any single test that would be able to rule in an infection in this specific patient population. A combination of a detailed clinical assessment and careful interpretation of collateral biochemical and microbiological test probably remains to be the optimal approach targeted to individual patients. The mechanism of inflammatory reaction in neutropenic patients and prompt detection of infection in those needs to be explored in future studies.

Conclusions

ATG administration was associated with a characteristic rapid surge in both PCT and CRP followed by a steady decline over the next 3 days. This increase was not associated with systemic infection. The number of ATG doses was not related to the peak PCT concentrations. ATG induced an increase in liver function tests but not in markers of renal function. PCT levels were not altered by renal and liver functions or WBC before conditioning. PCT seems to have no predictive value of future infectious complications. Both PCT and CRP have limited value in the diagnosis of infection during administration of ATG.

Key messages

- ATG administered during condition before haematopoietic stem cell transplantation triggered a marked increase in both PCT and CRP with peak at 24 h after administration, followed by a steady decline over the next 3 days. This increase was not associated with systemic infection.

- The number of ATG doses was not related to the peak PCT concentrations.
- ATG induced an increase in liver function tests but not in markers of renal function. PCT levels were not altered by renal and liver functions or WBC before conditioning.
- PCT seems to have no predictive value of future infectious complications.
- Both PCT and CRP have limited value in the diagnosis of infection during administration of ATG.

Abbreviations

ALT alanin aminotransferase

ATG anti-thymocyte globulin

CRP C-reactive protein

GFR glomerular filtration rate

GGT gamma-glutamyl transferase

IL interleukin

PCT procalcitonin

SIRS systemic inflammatory response syndrome

TNF tumor necrosis factor

WBC white blood cell count

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HB carried out the laboratory work and drafted the manuscript. MM was responsible for the patient care, ATG administration, sample timing and collection, and contributed to the creation of the manuscript. KM performed the statistical analysis. AV participated in the transplantation and contributed to the study design. AK and TZ participated in study design and helped to draft the manuscript. TD intellectually contributed to the creation of the manuscript.

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Figures and Tables legends:

Table 1. Basic descriptive characteristics of patients

Table 2. Interrelationship of PCT and other measured laboratory parameters

All measured significance levels are greater than 5% (n=26, Spearman's rank correlation test, *r*). PCT, procalcitonin; CRP, C-reactive protein; BILI, bilirubin; GGT, gamma-glutamyl transferase; ALT, alanin aminotransferase; GFR, glomerular filtration rate; CREAT, creatinine. Baseline = initial/pre-treatment value.

Table 3. Relative odds of post-ATG febrile complications according to PCT concentration on transplantation day (D_{TX})

The relative odds of post-ATG febrile/infectious complications did not increase significantly with each increasing quartile of baseline PCT concentration, such that patients in the highest versus lowest quartile did not have any increase in risk. After adjustment for CRP, the concentration of PCT remained unassociated with the risk of post-ATG febrile complications. PCT, procalcitonin; CRP, C-reactive protein; OR, odds ratio; CI, confidence interval.

Table 4. Procalcitonin and C-reactive protein concentration and white blood cell count in patients with sepsis

The dynamics of markers of PCT and CRP in patients who developed sepsis on days 7-11 after conditioning with ATG were different from increase in PCT and CRP during ATG conditioning. ATG, anti-thymocyte globulin; Dx, days after conditioning; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell count.

Figure 1. Dynamics of measured parameters during conditioning with ATG.

Values are displayed as mean ± SD. * $p < 0.05$ vs. baseline. Dx, day of conditioning regimen (please see text for details); ATG, anti-thymocyte globulin; PCT, procalcitonin (normal < 0.5 μg/L); CRP, C-reactive protein (normal < 7 mg/L); BILI, bilirubin (normal 2-17 μmol/L); GGT, gamma-glutamyl transferase (normal 0.1-0.68 μkat/L); ALT, alanin aminotransferase (normal 0.1-0.78 μkat/L); urea (normal 2.0-6.7 for females, 2.8-8.0 for males); CREAT, creatinine (normal, 44-104 μmol/L for females, 44-110 μmol/L for males); GFR, glomerular filtration rate (normal 1.5-2.0 mL/s); WBC, white blood cell count (4.3–10.8 x 10^9/L); SD, standard deviation.

Figure 2. The relationship between the number of ATG doses and PCT values

The black square markers represent the mean, the boxes standard deviation, and the whiskers min / max for each group. $p = 0.16$ between groups.

Table 1

Basic descriptive characteristics of patients

Gender		
	Males	14 (54 %)
	Females	12 (46 %)
Diagnosis		
	Acute Lymphoblastic Leukemia	4 (17%)
	Acute Myeloid Leukemia	7 (29%)
	Myeloproliferative Syndrome	5 (17%)
	Chronic Lymphatic Leukemia	2 (8%)
	Chronic Myeloid Leukemia	1 (4%)
	Myelodysplastic Syndrome	4(13%)
	Non-Hodgkin's Lymphoma	2 (8%)
	Hodgkin's Disease	1 (4%)
Age at ATG treatment		
	Mean (min, max)	43 (24, 62)
Number of ATG doses		
	2	11 (42%)
	3	12 (46%)
	4	3 (12%)
Post-ATG body temperature		
	Normal body temperature	20 (77%)
	Body temperature < 37.5 °C	5 (20%)
	Body temperature >37.5 °C	1 (3%)

Table 2

Interrelationship of PCT and other measured laboratory parameters

		PCT					
	r	**Baseline**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Baseline values of	**CRP**	0.04	0.17	0.06	0.29	0.32	0.03
	BILI	0.04	0.35	0.23	0.09	0.21	0.13
	GGT	0.03	0.22	0.07	0.22	0.19	0.02
	ALT	0.10	0.14	0.17	0.07	0.21	0.07
	GFR	0.12	0.32	0.08	0.04	0.09	0.16
	UREA	0.11	0.22	0.31	0.25	0.43	0.19
	CREAT	0.25	0.18	0.24	0.21	0.32	0.17

Table 3

Relative odds of post-ATG febrile complications according to PCT concentration on transplantation day (D_{TX})

	Quartile of PCT concentration (range, µg/L)				
	Q1 (< 1.6)	**Q2** (1.6 – 4.1)	**Q3** (4.1 – 14.9)	**Q4** (> 183)	**p-trend**
Crude matched pairs					
OR	1.00	1.10	1.05	1.10	
95% CI	-	0.03 - 0.85	0.25 - 5.87	2.51 - 59.87	0.095
p-value	-	0.26	0.11	0.09	
Adjusted for CRP					
OR	1.0	1.08	1.10	1.07	
95% CI	-	0.026 – 0.99	0.31 – 5.75	2.41 – 58.35	0.123
p-value	-	0.34	0.10	0.09	

Table 4

Procalcitonin and C-reactive protein concentration and white blood cell count in patients with sepsis

Patient 1	***D11***	***D12***	***D13***	***D14***	***D15***
PCT µg/L	1.7	13.4	58	43	36
CRP mg/L	124	150	173	295	300
WBC cells/µL	12 000	23 000	35 000	50 000	48 500
Patient 2	***D7***	***D8***	***D9***	***D10***	***D11***
PCT µg/L	7	8.1	5.3	3.1	1.1
CRP mg/L	304	311	201	182	110
WBC cells/µL	3 500	3 000	2 600	-	2 500
Patient 3	***D8***	***D9***	***D10***	***D11***	***D12***
PCT µg/L	8.3	5.4	3.2	1.8	1.1
CRP mg/L	270	330	370	260	180
WBC cells/µL	18 000	21 600	15 000	12 100	10 300

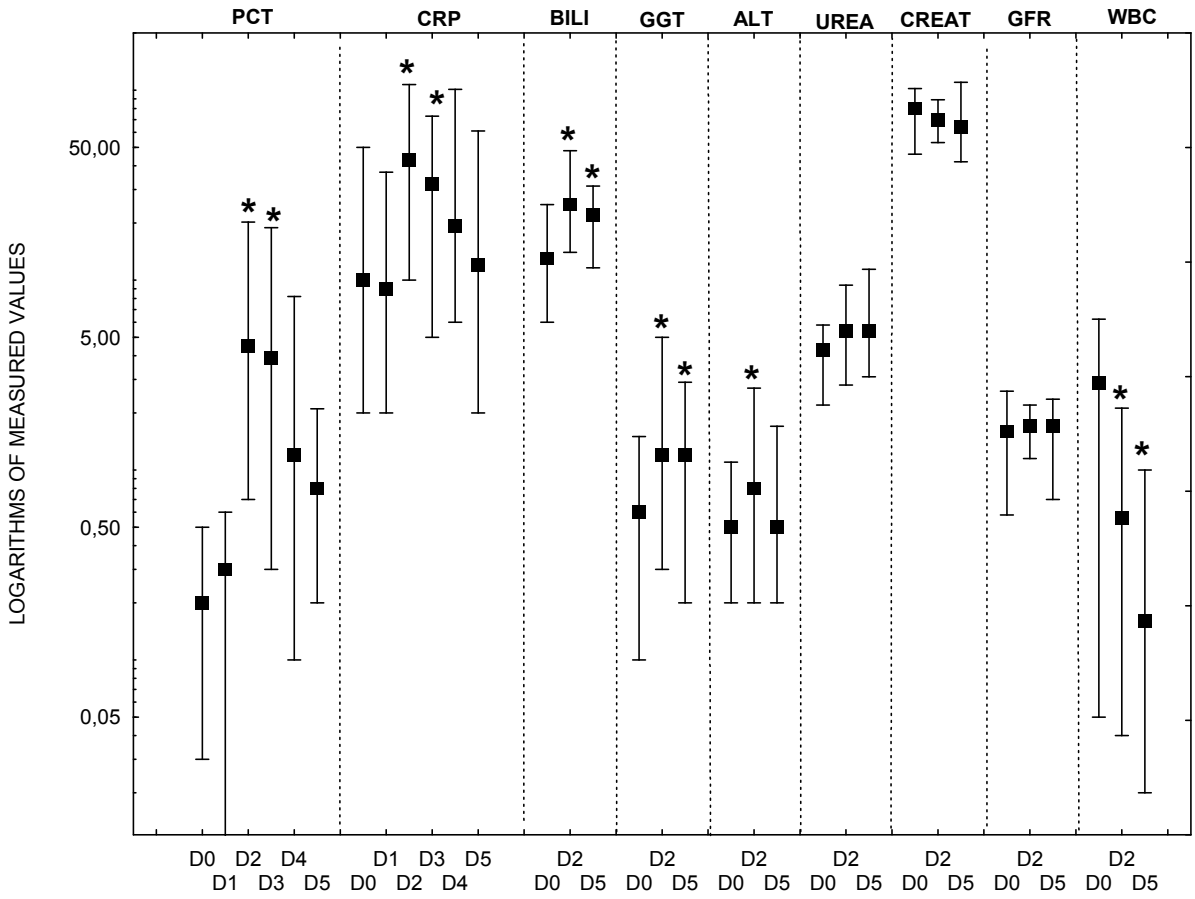
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Figure 1

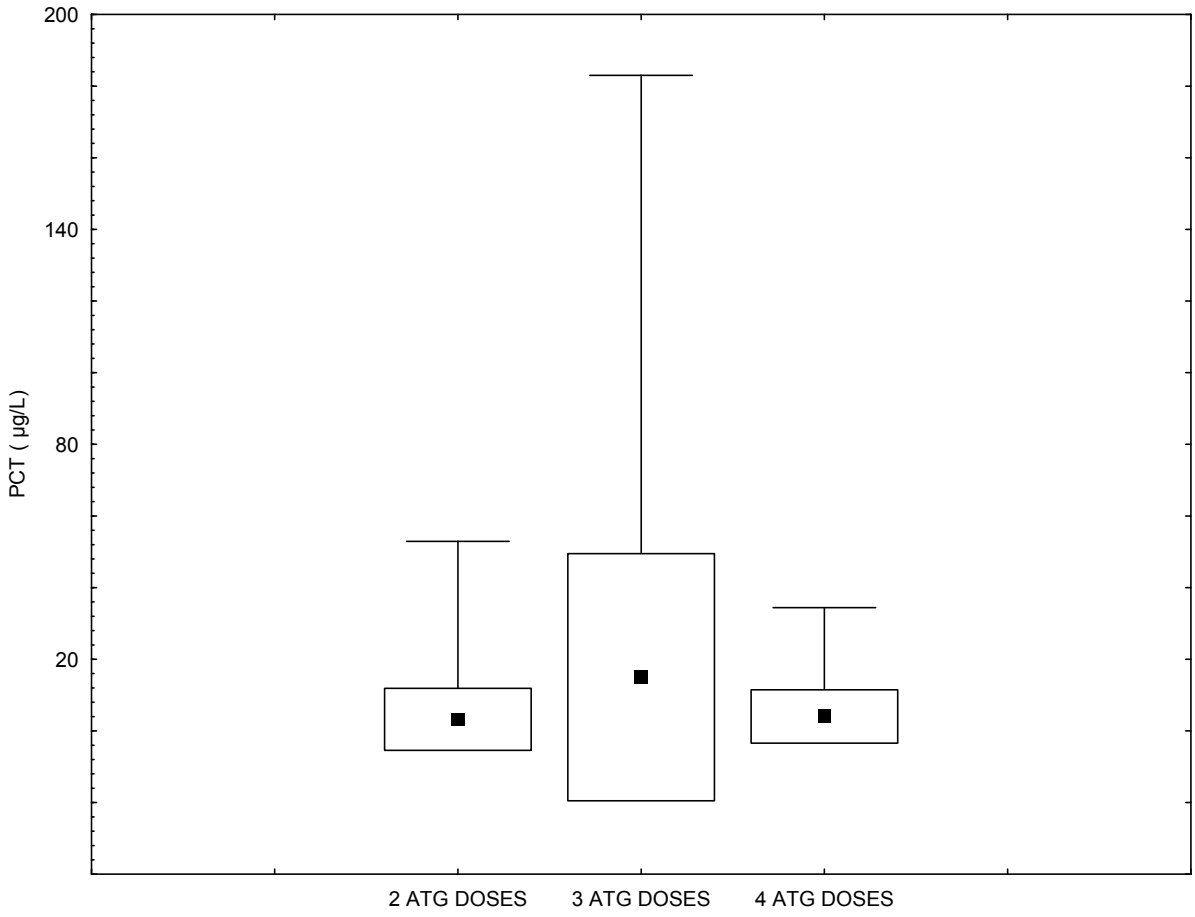

Figure 2