ORIGINAL PAPER

doi: 10.5455/medarh.2020.74.172-176
MED ARCH. 2020 JUN; 74(3): 172-176
RECEIVED: MAR 22, 2020 | ACCEPTED: MAY 28, 2020

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Comparison of the Effects of Allopurinol and Febuxostat on the Values of Triglycerides in Hyperuricemic Patients

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ABSTRACT

Introduction: Hyperuricemia is an independent risk factor for the development of many diseases. **Aim:** The aim of this paper is to compare the effects of allopurinol and febuxostat on the values of triglycerides and uric acid in hyperuricemic patients. **Methods:** This was a pharmacological-clinical retrospective-prospective study. The research sample comprised 50 examinees of both genders and different ages who were undergoing allopurinol (100 mg/day) or febuxostat (80 mg/day) therapy. Statistical Product and Service Solutions (SPSS) Software and Microsoft Excel were used for statistical analysis. **Results:** Examinees who were treated with allopurinol had a statistically significant decrease in uric acid concentrations (by 126.28 ± 20.36 μmol/l) at the end of the observation compared to the initial values ($p = 0.006$). Examinees who were treated with febuxostat had a statistically significant decrease in uric acid concentrations (by 252.80 ± 94.17 μmol/l) at the end of the observation compared to the initial values ($p = 0.001$). The initial value of triglycerides was 1.58 ± 0.64 mmol/l in allopurinol-treated examinees, and 1.60 ± 0.52 mmol/l in febuxostat-treated examinees. After three and six months of allopurinol use, there was a statistically significant increase in triglyceride values ($p = 0.046$ and $p = 0.042$, respectively). A statistically significant decrease in triglyceride values (by 0.16 ± 0.10 mmol/l) was noted after three months of febuxostat use ($p = 0.012$). **Conclusion:** The results of this research confirmed the previous findings and pointed out the positive pharmacological effects of allopurinol and febuxostat.

Keywords: hyperuricemia, allopurinol, febuxostat, uric acid, triglycerides.

1. INTRODUCTION

Serum uric acid concentration as a potential marker of cerebrovascular, cardiovascular and diseases such as arthritis and nephrolithiasis, and its association with metabolic syndrome, has been in the focus of medical research for 50 years (1-4). Hyperuricemia occurs when serum uric acid concentration is 416 μmol/l or above (4). Hyperuricemic patients are often diagnosed with hyperlipidemia. Correlation between serum urate and lipid values is interesting, but the results of some studies regarding this are contradictory. Certain studies have shown a significant link between serum lipid values and hyperuricemia in the examinees with metabolic syndrome, with triglycerides, total cholesterol and high-density lipoprotein (HDL) being positively and low-density lipoprotein (LDL) negatively correlated with hyperuricemia (5-9). Some studies on animal models have shown a significant link between serum uric acid and triglyceride values (10, 11). Heimbach and associates showed that drug-altered uric acid values were poorly correlated with triglyceride and LDL values (12). Results of many studies have suggested that allopurinol and febuxostat have undoubted efficacy in the treatment of hyperuricemia and gout (13-16). Target serum uric acid value can be achieved in 22% of the allopurinol-treated examinees (300 mg/day) and 48% of the febuxostat-treated examinees (80 mg/day) (17). Zhang and associates studied the effects of allopurinol and febuxostat on serum lipid values in the examinees with gout. There was no significant difference regarding this before and after the allopurinol treatment, while there was a significant decrease in total cholesterol, triglyceride and LDL values, and a significant increase in HDL values after the febuxostat treatment (18).

2. AIM

The aim of this paper is to compare the effects of the conventional therapy of hyperuricemia (allopurinol) and its novel therapy (febuxostat) on the values of triglycerides and uric acid in hyperuricemic patients.

3. MATERIALS AND METHODS

This was a pharmacological-clinical retrospective-prospective study. Materials were collected at the clinical center, general hospital, family medicine units, and pharmacies. The research sample comprised 50 examinees of both genders and different ages who were undergoing allopurinol or febuxostat therapy. Twenty-five of them (group I) were taking allopurinol (100 mg/day), and the other 25 (group II) were taking febuxostat (80 mg/day).

The inclusion criteria were:

- Verification of hyperuricemia diagnosis by a physician, based on laboratory diagnostics;
- Data availability regarding treatment and its possible complications;
- Availability of indicators by gender and age, and anamnestic data.

Uric acid and triglyceride values were analyzed in serum samples, at the beginning (first measurement), and after three (second measurement) and six (third measurement) months of drug use. Statistical Product and Service Solutions (SPSS) Software for Windows (version 20.0, SPSS Inc., Chicago, Illinois, the United States of America) and Microsoft Excel (version 13, Microsoft Corporation, Redmond, Washington, the United States of America) were used for statistical analysis. Alpha (significance) level was 0.05.

4. RESULTS

In both groups, there were 14 (56%) male and 11 (44%) female examinees. Chi-squared test (χ^2-test) did not reveal a statistically significant difference in the gender-structure of the examinees between the experimental groups ($\chi^2 = 0.011$; $p = 0.609$).

The average age of the examinees was 70.84 ± 14.51 years (from 37 to 88) in group I, and 71.84 ± 11.77 years (from 38 to 84) in group II. Using Analysis of variance (ANOVA), no statistically significant difference was observed in the average age of the examinees between the experimental groups ($F = 0.072$; $p = 0.790$).

With the diagnosis of gout, there were 15 (60%) examinees in group I, and 18 (72%) in group II. Gout associated with metabolic syndrome was diagnosed in ten (40%) examinees in group I, and seven (28%) in group II. Using χ^2-test, no statistically significant difference was found regarding the established clinical diagnoses between the experimental groups ($\chi^2 = 0.786$; $p = 0.276$).

Analysis of Uric Acid and Triglyceride Values in the Examinees Undergoing Allopurinol Therapy

In Table 1, the initial values of uric acid and triglycerides in the examinees who were taking allopurinol, as well as their values after three and six months of drug use are presented. After the second measurement, a statistically significant decrease in uric acid value was found ($p = 0.015$), as well as a statistically significant increase in triglyceride value ($p = 0.046$). There was no statistically significant difference in uric acid and triglyceride values between the second and the third measurement ($p = 0.344$ and $p = 0.301$, respectively). At the end of the observation, a decrease in uric acid value was statistically significant ($p = 0.006$), as well as an increase in triglyceride value ($p = 0.042$).

Analysis of Uric Acid and Triglyceride Values in the Examinees Undergoing Febuxostat Therapy

In Table 2, the initial values of uric acid and triglycerides in the examinees who were taking febuxostat, as well as their values after three and six months of drug use are presented. After the second measurement, a statistically significant decrease in uric acid and triglyceride values was found ($p = 0.001$ and $p = 0.012$, respectively). There was no statistically significant difference in uric acid and triglyceride values between the second and the third measurement ($p = 0.089$ and $p = 0.212$, respectively). At the end of the observation, a decrease in uric acid value was statistically significant ($p = 0.001$), but not in triglyceride value ($p = 0.542$).

Observation period	Uric acid		Triglycerides	
	X^a (μmol/l)	SD^b (μmol/l)	X^a (mmol/l)	SD^b (mmol/l)
From the beginning to 3rd month	522.60	147.99	1.58	0.64
	430.48	201.25	1.77	0.70
From 3rd month to 6th month	430.48	201.25	1.77	0.70
	396.32	138.97	1.92	1.04
From the beginning to 6th month	522.60	147.99	1.58	0.64
	396.32	138.97	1.92	1.04

Observation period	Paired Differences							
	Uric acid				Triglycerides			
	X^a (μmol/l)	SD^b (μmol/l)	t	p value	X^a (mmol/l)	SD^b (mmol/l)	t	p value
From the beginning to 3rd month	92.12	17.29	2.628	0.015	-0.19	0.16	-2.091	0.046
From 3rd month to 6th month	34.16	17.82	0.966	0.344	-0.14	0.07	-1.055	0.301
From the beginning to 6th month	126.28	20.36	3.016	0.006	-0.33	0.27	-2.935	0.042

Table 1. Average values of uric acid and triglycerides in the examinees treated with allopurinol. [a]X – arithmetic mean; [b]SD – standard deviation

Comparison of Uric Acid and Triglyceride Values with Regard to the Experimental Groups

The initial value of uric acid was 522.60 ± 147.99 μmol/l in group I, and 577.04 ± 120.25 μmol/l in group II. After conducting ANOVA test, no statistically significant difference was determined (p = 0.160). After the second measurement, a statistically significant difference was determined (p = 0.031), the mean value of uric acid was 430.48 ± 201.25 μmol/l in group I, and 338.12 ± 50.40 μmol/l in group II. At the end of the observation, a statistically significant difference was determined (p = 0.017), the mean value of uric acid was 396.32 ± 138.97 μmol/l in group I, and 324.24 ± 45.77 μmol/l in group II (Figure 1).

The initial value of triglycerides was 1.58 ± 0.64 mmol/l in group I, and 1.60 ± 0.52 mmol/l in group II. After conducting ANOVA test, no statistically significant difference was determined (p = 0.903). After the second measurement, no statistically significant difference was determined (p = 0.065), the mean value of triglycerides was 1.77 ± 0.70 mmol/l in group I, and 1.43 ± 0.56 mmol/l in group II. At the end of the observation, no statistically significant difference was determined (p = 0.123), the mean value of triglycerides was 1.92 ± 1.04 mmol/l in group I, and 1.54 ± 0.59 mmol/l in group II (Figure 2).

Comparison of Uric Acid and Triglyceride Values with Regard to the Gender-Structure of the Examinees

The mean value of uric acid at the beginning of the observation in both groups showed no statistically significant difference with regard to the gender-structure of the examinees (p = 0.090 and p = 0.710, respectively). At the end of the observation, a decrease in uric acid values was noted, but no statistically significant difference was determined between male and female examinees who were undergoing allopurinol or febuxostat therapy (p = 0.836 and p = 0.840, respectively).

The mean value of triglycerides at the beginning of the observation in both groups showed no statistically significant difference with regard to the gender-structure of the examinees (p = 0.692 and p = 0.694, respectively). At the end of the observation, an increase in triglyceride values was noted, but no statistically significant difference was determined between male and female examinees who were undergoing allopurinol therapy (p = 0.718), whereas a decrease in female examinees and an increase in male examinees in triglyceride values were noted, but no statistically significant difference was determined between male and female examinees who were undergoing febuxostat therapy (p = 0.125).

Observation period	Uric acid		Triglycerides	
	X^a (μmol/l)	SD^b (μmol/l)	X^a (mmol/l)	SD^b (mmol/l)
From the beginning to 3rd month	577.04	120.25	1.60	0.52
	338.12	50.40	1.43	0.56
From 3rd month to 6th month	338.12	50.40	1.43	0.56
	324.24	45.77	1.54	0.59
From the beginning to 6th month	577.04	120.25	1.60	0.52
	324.24	45.77	1.54	0.59

Observation period	Paired Differences							
	Uric acid				Triglycerides			
	X^a (μmol/l)	SD^b (μmol/l)	t	p value	X^a (mmol/l)	SD^b (mmol/l)	t	p value
From the beginning to 3rd month	238.92	89.00	13.4	0.001	0.16	0.10	2.717	0.012
From 3rd month to 6th month	13.88	1.80	1.18	0.089	-0.10	0.09	-1.282	0.212
From the beginning to 6th month	252.80	94.17	13.4	0.001	0.06	0.03	0.619	0.542

Table 2. Average values of uric acid and triglycerides in the examinees treated with febuxostat. ^{a}X – arithmetic mean; ^{b}SD – standard deviation

Serum values	Drug	Observation period	Gout	Gout + metabolic syndrome	p value
Uric acid (μmol/l)	Allopurinol	Beginning of the study	537.26 ± 153.58	500.60 ± 144.28	0.555
		End of the study	385.00 ± 165.32	413.30 ± 91.93	0.628
	Febuxostat	Beginning of the study	601.00 ± 127.89	515.42 ± 73.12	0.112
		End of the study	332.33 ± 44.79	303.42 ± 44.63	0.161
Triglycerides (mmol/l)	Allopurinol	Beginning of the study	1.37 ± 0.55	1.90 ± 0.66	0.042
		End of the study	1.76 ± 1.14	2.15 ± 0.87	0.364
	Febuxostat	Beginning of the study	1.38 ± 0.40	2.16 ± 0.37	0.001
		End of the study	1.33 ± 0.52	2.07 ± 0.41	0.003

Table 3. Mean values of uric acid and triglycerides with regard to the established clinical diagnoses and the observation period in the examinees treated with allopurinol or febuxostat

Comparison of Uric Acid and Triglyceride Values with Regard to the Established Clinical Diagnoses

No statistically significant difference was noted in uric acid values in the examinees with the diagnosis of only gout and both gout and metabolic syndrome in both groups at the beginning and at the end of the observation. At the beginning of the observation, the examinees diagnosed with gout and treated with allopurinol

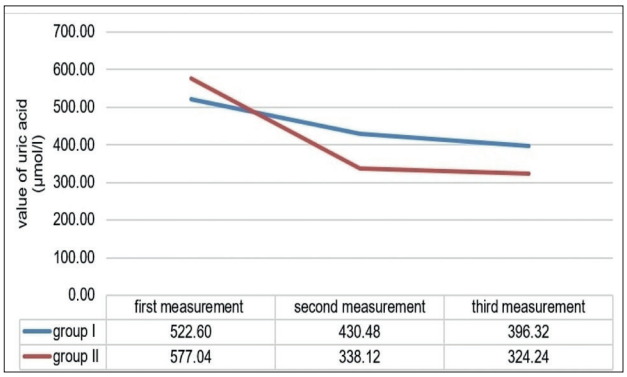

Figure 1.

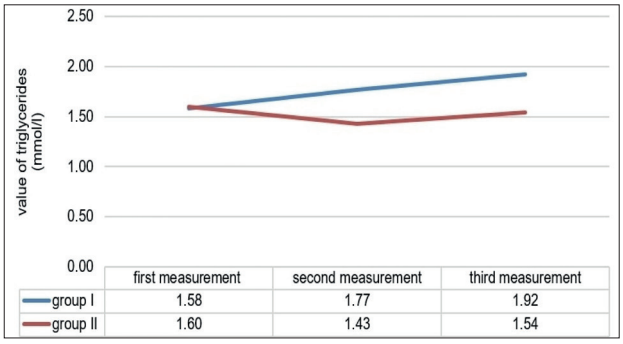

Figure 2. Mean values of triglycerides with regard to the experimental groups

showed significantly lower triglyceride values compared to the examinees diagnosed with gout and metabolic syndrome and treated with allopurinol ($p = 0.042$), but at the end of the observation, there was no statistically significant difference in triglyceride values ($p = 0.364$). The examinees diagnosed with gout and metabolic syndrome and treated with febuxostat showed significantly higher triglyceride values compared to the examinees diagnosed with gout and treated with febuxostat at the beginning and at the end of the observation ($p = 0.001$ and $p = 0.003$, respectively) (Table 3).

5. DISCUSSION

Since 10% of the patients cannot tolerate allopurinol because of the occurrence of hypersensitivity and vasculitis, or its contraindication in the renal insufficiency, febuxostat has become an efficient replacement (19). Target serum urate values are more frequently achieved with febuxostat than with allopurinol because its inhibition of xanthine oxidoreductase (XOR) is more potent (20). Since the main aim of febuxostat therapy is to prevent and reduce the incidence of new gout attacks, its therapeutic application has to be continued for a week or two after an acute attack. During the first six months of febuxostat therapy, new gout attacks are quite often, so additional therapeutic agents, such as non-steroid anti-inflammatory drugs (NSAID) or colchicine, should be used. Results of some studies have demonstrated the efficacy of febuxostat in the treatment of hyperuricemia and gout, as well as conditions with detected renal insufficiency (13-15). Results of the research presented in this paper confirmed the findings of previous studies. Examinees who were treated with allopurinol or febuxostat had significantly lower uric acid concentrations, compared to its initial concentrations, after three and six months of drug use. Better effect of febuxostat on the reduction of uric acid values were also confirmed because uric acid values were significantly lower after three and six months with febuxostat (80 mg/day) than with allopurinol (100 mg/day). Gender did not influence the response to XOR inhibitors, which was consistent with the results of the study conducted by Wanten and associates (21). A significant increase in triglyceride values was observed after three and six months of allopurinol use. In the study conducted by Žiga and associates, the mean value of triglycerides was not significantly different compared to their initial value ($p = 0.846$), as well as after three months of allopurinol use ($p = 0.153$), whereas after six months, the mean value of triglycerides was significantly higher compared to their initial value ($p = 0.047$) (9). The results of the research presented in this paper demonstrated a direct correlation between serum triglyceride values and hyperuricemia in patients with metabolic syndrome. Also, a significant decrease in triglyceride values was observed after three months of febuxostat use, but not after six months. According to some studies, uric acid-lowering therapy has beneficial effects on hyperlipidemia in patients with gout (22, 23). Wu and associates showed that febuxostat significantly decreased cholesterol and triglyceride values in the patients who were not taking lipid-lowering therapy, whereas allopurinol and benzbromarone modestly decreased triglyceride values, but cholesterol values remained unaffected.

6. CONCLUSION

Allopurinol and febuxostat both cause a significant decrease in uric acid values in hyperuricemic patients after three and six months of therapy. This decrease is greater with febuxostat, indicating its better efficacy. A significant increase in triglyceride values is noted after three and six months of allopurinol use, whereas a significant decrease in triglyceride values is noted after three months of febuxostat use, but not after six months.

- **Acknowledgements**: The authors are very grateful to all subjects who participated in this research and to directors and employees of the Clinical center University of Sarajevo, General hospital "Prim. dr. Abdulah Nakaš", family medicine units of Health center Sarajevo, and pharmacies, for providing necessary facilities and equipment to carry out this research.
- **Declaration of patient consent**: The authors certify that each subject gave informed consent.
- **Ethical approval**: The authors certify that the research protocol was in accordance with the ethical standards of the relevant Ethics review committees and the Helsinki Declaration.
- **Authors' contribution**: Each author gave a substantial contribution to the conception and design of the work, the acquisition, analysis and interpretation of the data, and the drafting and critical revision of the work for important intellectual content. Each author gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

- **Conflict of interest**: The authors declare that there was no conflict of interest.
- **Financial support and sponsorship**: The authors declare that there was no financial support and sponsorship.

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