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Influence of leflunomide on serum uric acid levels in patients with rheumatoid arthritis

Influência da leflunomida nos níveis de ácido úrico sérico em pacientes com artrite reumatoide

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ABSTRACT

Introduction: Inflammation is a common component of autoimmune diseases such as rheumatoid arthritis. There is increasing evidence of the role of serum uric acid in the inflammatory process of rheumatoid arthritis and its possible influence on disease activity.

Objective: To correlate serum uric acid levels with disease activity, worse prognostic factors and medications in use in patients with rheumatoid arthritis.

Method: Data related to epidemiology, symptoms, pharmacological treatments and disease scores from medical records of 105 patients with rheumatoid arthritis followed at the rheumatology outpatient clinic were collected.

Result: The mean serum uric acid value in patients was 3.4 mg/dL and there was no significance between the trained biomarker and disease activity scores. The association between the biomarker with hypertension (p = 0.0014), diabetes mellitus (p = 0.058), leflunomide (p = 0.0276) and JAK inhibitors (p = 0.02) showed significance. However, a significant association was only observed between lower levels of serum uric acid and the use of leflunomide (p = 0.0192; t = -2.382).

Conclusion: Variation in the biomarker does not demonstrate an impact on disease activity. Patients using leflunomide showed reduced levels of the biomarker, reinforcing its hypouricemic effect.

KEYWORDS: Rheumatology. Arthritis. Uric acid marker serum. Leflunomide.

Central Message

There are potential diagnostic biomarkers of rheumatoid arthritis, which can be obtained by dosages, such as rheumatoid factor, antiprotein antibodies, and citrullinated peptides - anti-CCP. It is pointed out that serum uric acid (AUS) may also be an important biomarker for the disease. It is the final catabolic of purine metabolism, and growing evidence points to an important role in the inflammatory process, as it stimulates the production of pro-inflammatory cytokines.

Perspective

This study showed that although some studies indicate that high serum uric acid levels are associated with worse outcomes in the course of rheumatoid arthritis, this finding did not modify the activity of the disease. On the other hand, the use of leflunomide had a hypouricemide effect on individuals, reinforcing its action on the renal excretion of this compound.

RESUMO

Introdução: Inflamação é componente comum das doenças autoimunes como a artrite reumatoide. Há crescentes evidências do papel dele sérico no seu processo inflamatório e possível influência na atividade da doença.

Objetivo: Correlacionar níveis séricos de ácido úrico à atividade da doença, aos fatores de pior prognóstico e medicamentos em uso em pacientes com essa artrite.

Método: Coletou-se dados relacionados à epidemiologia, sintomatologia, tratamentos farmacológicos e escores de doença de prontuários de 105 pacientes com artrite reumatoide, correlacionando-os com os níveis séricos de ácido úrico, como biomarcador.

Resultado: O valor mediano de ácido úrico sérico foi de 3,4 mg/dL e não houve significância entre ele e scores de atividade de doença. Ao associá-lo com hipertensão (p = 0,0014), diabete melito (p = 0,058), leflunomida (p = 0,0276) e inibidores de JAK (p = 0,02) observou-se significância. Contudo, demonstrou-se correlação significativa apenas entre menores taxas de ácido úrico sérico e o uso de leflunomida (p = 0,0192; t = -2,382).

Conclusão: A variação nos níveis séricos de ácido úrico não demonstrou impacto na atividade da doença. Os pacientes em uso de leflunomida apresentaram níveis reduzidos do biomarcador, reforçando seu efeito hipouricêmico.

PALAVRAS-CHAVE: Reumatologia. Artrite reumatoide. Ácido úrico, biomarcador sérico. Leflunomida.

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INTRODUCTION

Inflammation is a common component of several rheumatology diseases, and is even present in rheumatoid arthritis (RA).[1] This disease, in addition to being inflammatory, is autoimmune, chronic, progressive and causes polyarticular involvement.[2] In order to diagnose, it is recommended to combine clinical practice with complementary tests, and isolated tests do not establish a diagnosis.[3]

There are potential biomarkers in its diagnosis, which can be obtained by dosages; they are: rheumatoid factor (RF), anti-protein antibodies and citrullinated peptides (ACPA), as is the case of anti-CCP.[4]

It is pointed out that serum uric acid (AUS) may also be an important biomarker for rheumatoid arthritis. Uric acid (UA) is the final catabolic of purine metabolism,5 and growing evidence points to its important role in the inflammatory process, as it stimulates the production of pro-inflammatory cytokines, such as IL-6, TNF-α and IL-1β.[6]

Thus, it is necessary to correlate their serum levels with disease activity, worse prognostic factors, and medications in use in RA, in order to elucidate their influence on these components.

The association of AUS with systemic inflammation and disease activity in RA remains controversial, since there are studies in the literature that corroborate it and others that weaken it. Also, it is necessary to take into account which is the disease-modifying drug with which the patient is treated.

A South Korean study identified that AU may have no influence on the systemic inflammation of RA in patients using leflunomide, since this drug potentially reduces serum AU concentrations, by virtue of increasing its renal excretion due to its mechanism of action.[6]

Another study, in a Brazilian population with RA, noted that treatment with leflunomide was associated with lower AUS levels and also found that patients with metabolic syndrome had higher AUS values.[7]

An Egyptian study observed that there was a prevalence of higher levels of AUS in patients with RA, which may be a potential marker of severe synovial inflammation. However, there was no significant association between disease-modifying drugs and AUS levels; however, treatment with high doses of glucocorticoids was associated with their higher levels.[8]

Regarding anti-TNF's, a study evaluated whether therapy with these medications altered AUS levels in patients with systemic autoimmune rheumatic diseases, including RA, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis. At the end of 3 months of treatment, it was noted that AUS values increased significantly.[9]

Regarding the impact of methotrexate use on AUS levels, a Canadian study evaluated that patients with early RA had reductions in AUS values after treatment with this disease-modifying drug.[10]

Thus, the aim of this RA study was to correlate serum UA levels with disease activity, worse prognostic factors, and medications in use.

METHOD

This study was approved by the Human Research Ethics Committee of the Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brazil – CAAE no. 63753122.0.0000.0103. It is retrospective longitudinal. Data were collected from the medical records of 105 patients with RA who were following the disease at the Rheumatology Outpatient Clinic of the Mackenzie Evangelical University Hospital, Curitiba, PR, Brazil. The following data were collected from the medical records: epidemiological (gender, age, ethnicity, age at diagnosis, duration of disease, comorbidities), disease (presence of nodules, pneumonitis, rheumatoid factor, anti-CCP), immunosuppressive medications in use (corticosteroids and disease modifiers), disease activity (DAS28, ESR, DAS28 CRP, CDAI and SDAI) and laboratory data - erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), uric acid, lipid profile, fasting glucose, urea, creatinine, oxaloacetic (ROT) and pyruvic (PGT) transaminases. AUS was considered to be below 7 mg/dL for men and 6 mg/dL for women.

RESULT

Between October 2022 and March 2023, data were collected from 105 medical records of patients with RA who met the inclusion and exclusion criteria of the present study.

Of the 105 patients, the median age was 59 years (53-66), 88.6% (n = 91) were women, and of these, 82.4% (n = 75) were over 50 years of age. Caucasian ethnicity was present in 83% (n = 88), with a median disease duration of 12 years (8-19). Regarding lifestyle habits, a little more than 1/4 of the group (25.7%) had a recent history of smoking. In addition, 47.6% had systemic arterial hypertension (n = 50) and 20% (n = 21) diabetes mellitus as comorbidities.

Of the variables related to RA severity, 70.4% (n = 74) had positive rheumatoid factor (RF), 12.4% (n = 13) rheumatoid nodules, and 20.9% (n = 22) pneumonitis.

The medications in use during the collection of the tests are described in the Table.

TABLE – Medications in use during laboratory test collection

Drug	n (%)
Corticosteroid (median 5 mg/day)	46 (43,8)
Methotrexate	39 (37,1)
Leflunomide	57 (54)
Anti-TNF	21 (20)
Tocilizumab	14 (13,3)
Jak Inhibitor	23 (21,9)

Statistical analysis

When the independent variables were tested, there was a correlation between lower AUS indices and leflunomide use (p = 0.0192; t = -2.382). On the other hand, the correlation study between disease activity scores and AUS levels did not obtain statistical significance.

DISCUSSION

The present study showed that, although some studies indicate that high serum levels of UA are associated with worse outcomes in the course of RA, this finding did not modify the disease activity. The use of leflunomide had a hypouricemide effect on individuals, reinforcing its action on the renal excretion of this compound, which has already been pointed out in other studies.

Choe and Kim6 found similar results when they pointed out that the use of leflunomide reduced the serum concentration of AU, in addition to suggesting that uricemia was not associated with inflammatory responses in RA, since the use of such therapy, as well as its effects on AU, did not alter the acute phase reactants (ESR and CRP).

However, further studies are needed in order to better elucidate the potential hypouricemian effect of this medication and its possible benefits to other comorbidities.

CONCLUSION

The variation in the biomarker did not demonstrate an impact on RA activity. Patients using leflunomide had reduced levels of the biomarker, reinforcing its hypouricemic effect.

Authors' contributions

Conceptualization: Camila Tonet
Methodology: Maria Fernanda Corrêa Vieira
Project Administration: Barbara Stadler Kahlow
Writing (original draft): All authors
Writing (proofreading and editing): All authors

REFERENCES

1. Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020;9(4):880. https://doi.org/10.3390/cells9040880
2. Da Mota LMH, Laurindo IMM, Neto-Santos L dos. Artrite reumatoide inicial - conceitos. Rev Assoc Med Bras. 2010;56(2):227-29. https://doi.org/10.1590/S0104-42302010000200024
3. Sociedade Brasileira de Reumatologia, Sociedade Brasileira de Pneumologia e Tisiologia, Colégio Brasileiro de Radiologia, Da Mota LMH. Diretrizes para o diagnóstico da artrite reumatoide guidelines for the diagnosis of rheumatoid arthritis. Rev Bras Reumatol. 2013;53(2):141-57.
4. Goeldner I, Skare TL, Reason ITM, Ramos S, Utiyama R. Artrite reumatoide: uma visão atual. J Bras Patol Med Lab. 2011;47(5)495-503.
5. Wang Z, Wang W, Xiang T, Gong B, Xie J. Serum uric acid as a diagnostic biomarker for rheumatoid arthritis-associated interstitial lung disease. Inflammation. 2022;45(4):1800-14. https://doi.org/10.1007/s10753-022-01661-w
6. Choe JY, Kim SK. Association between serum uric acid and inflammation in rheumatoid arthritis: perspective on lowering serum uric acid of leflunomide. Clin Chim Acta. 2015;438:29-34. https://doi.org/10.1016/j.cca.2014.07.039
7. Costa NT, Scavuzzi BM, Iriyoda TMV, Lozovoy MAB, Alfieri DF, Medeiros FA, et al. Metabolic syndrome and the decreased levels of uric acid by leflunomide favor redox imbalance in patients with rheumatoid arthritis. Clin Exp Med. 2018;18(3):363-72. https://doi.org/10.1007/s10238-018-0500-y
8. Nada D, Gaber R, Mahmoud AS, Elkhouly R, Alashkar D. Hyperuricemia among egyptian rheumatoid arthritis patients: Is it an association or an inflammatory marker? A cross-sectional observational study. Open Access Rheumatol. 2021;13:305-14. https://doi.org/10.2147/OARRR.S331488
9. Hasikova L, Pavlikova M, Hulejova H, Kozlik P, Kalikova K, Mahajan A, et al. Serum uric acid increases in patients with systemic autoimmune rheumatic diseases after 3 months of treatment with TNF inhibitors. Rheumatol Int. 2019;39(10):1749-57. https://doi.org/10.1007/s00296-019-04394-6
10. Lee JJ, Bykerk VP, Dresser GK, Boire G, Haraoui B, Hitchon C, et al. Reduction in serum uric acid may be related to methotrexate efficacy in early rheumatoid arthritis: data from the Canadian Early Arthritis Cohort (CATCH). Clin Med Insights Arthritis Musculoskelet Disord. 2016;9:37-43. https://doi.org/10.4137/CMAMD.S38092