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Original Article

Systematic Review of the Value of Ultrasound and Magnetic Resonance Musculoskeletal Imaging in the Evaluation of Response to Treatment of Gout☆

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ABSTRACT

Background: Imaging may be useful for monitoring response to therapy. Within the OMERACT proposal for the core set domains for outcome measures in chronic gout, serum urate levels, recurrence of gouty flares, tophus regression, and joint damage imaging have been included, among other proposed issues.
Objectives: To perform a systematic literature review of the usefulness of magnetic resonance imaging (MRI) and ultrasound (US) on assessment of treatment response in patients with gout.
Methods: MEDLINE, EMBASE, Cochrane Library (up to February 2012), and abstracts presented at the 2010 and 2011 meetings of the American College of Rheumatology and European League Against Rheumatism were searched for treatment studies of any duration and therapeutic options, examining the ability of MRI/US to assess treatment response in gouty patients. Meta-analyses, systematic reviews, randomized clinical trials, cohort and case-control studies and validation studies were included. Quality was appraised using validated scales.
Results: There were only 3 US published studies in the literature that analyzed US utility on assessment of response to treatment in patients with gout. All of them were prospective case studies with a small number of patients and they were reviewed in a detailed manner. A total of 36 patients with gout were examined with US. All of them had a baseline serum urate >6 mg/dL. US features of gout (double contour sign, hyperechoic spots in synovial fluid, hyperechoic cloudy areas, tophus diameter and volume) achieved significant reduction in patients who reached the objective of uricemia ≤6 mg/dL in all the studies; however, patients in whom levels did not drop below 6 mg/dL had no change of US features of gout. Other parameters evaluated in one study included ESR, CRP, number of tender joints (TRN), number of swollen joints, and pain score (SP). All of them decreased with uricemia reduction, but only TRN and SP were statistically significant. No data were found on the value of MRI on treatment response assessment in patients with gout.
Conclusions: The improvement in ultrasound features shows concurrent validity with uric acid reduction. According to the published evidence, US can be a useful tool for monitoring treatment of gouty patients, although more research is needed. The value of MRI on treatment response assessment in patients with gout remains to be determined.

Revisión sistemática sobre el valor de la ecografía y la resonancia magnética nuclear musculoesqueléticas en la evaluación de la respuesta al tratamiento en la gota

Palabras clave:
Gota
Respuesta al tratamiento

RESUMEN

Objetivos: Evaluar sistemáticamente la evidencia publicada en relación con la utilidad de la ecografía y de la resonancia magnética nuclear (RMN) en la evaluación de la respuesta al tratamiento en pacientes con artritis por depósito de cristales de urato monosódico.

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Resonancia magnética
Ecografía

Métodos: Revisión sistemática. Se definió una estrategia de búsqueda bibliográfica sensible en MEDLINE (desde 1960), EMBASE (desde 1980) y Cochrane Library (Central) y búsqueda manual en lo publicado en congresos internacionales (EULAR, ACR), seleccionando estudios que evaluasen la respuesta al tratamiento de los pacientes con gota (AINE, hipouricemiantes, etc., independientemente del tipo, de la dosis y de la duración del tratamiento e independientemente del criterio seleccionado para el diagnóstico, el tipo y el número de articulaciones afectadas) mediante pruebas de imagen (ecografía y/o RMN). Se seleccionaron metaanálisis, revisiones sistemáticas, ensayos clínicos, cohortes de calidad y estudios de validación.
Resultados: Los estudios incluidos fueron 3 series de casos, de diseño prospectivo, en los que se analizó un total de 36 pacientes con artritis gotosa y en los que se evaluó la respuesta al tratamiento hipouricemiante mediante ecografía. No hubo ningún estudio que analizara la respuesta al tratamiento hipouricemiante con RMN. Todos los pacientes incluidos tenían valores basales de uricemia por encima de las recomendaciones EULAR. La mejoría en los hallazgos ecográficos se correlacionó con la reducción de los valores séricos de ácido úrico en todos los estudios.
Conclusiones: El uso de la ecografía parece útil en la evaluación de la respuesta al tratamiento hipouricemiante en los pacientes con artritis gotosa (nivel de evidencia 3a; grado de recomendación B). Actualmente no se dispone de ninguna evidencia para analizar la utilidad de la RMN en la evaluación del tratamiento de los pacientes con artritis gotosa.

Introduction

Gout is caused by the formation and deposition of monosodium urate crystals (MSU) in joints, or by forming usually extra-articular nodules called tophi. For the crystals to form, uric acid concentrations above 6.8 mg/dL in blood are required, which is the saturation point for[1,2] MSU .Once formed, the crystals remain in the joint cavity indefinitely while hyperuricemia, persists and over time the deposit increases and affecting more joints. However, the deposition of crystals may be reversed and, if the concentration of uric acid decreases, the crystals are dissolved and gout can be considered cured.[3,4]

As recommended by the EULAR working group for the treatment of gout, hypouricemic treatment goal is to promote the dissolution of the crystals and prevent their formation; this is achieved by maintaining a serum uric acid concentration below the saturation point for MSU: $\leq$6 mg/dL (360 $\leq$ mol/L).[5,6]

Various trials and cohort studies have shown an inverse correlation between serum uric acid levels during treatment and the speed with which the subcutaneous tophi[7,8] are reduced. The reduction of uric acid below 6 mg/dL is associated with not only a progressive reduction of subcutaneous tophi, but also reducing the size of the deep tophi, not accessible to physical examination and yet others detectable by imaging techniques such as ultrasound and magnetic resonance imaging (MRI).[8] Since these techniques are valid for determining the size of tophi and their location, it is of great interest to know their usefulness in evaluating the effectiveness of hypouricemic treatment, which helps decide not only when to use hipouricemic agents in patients with gout but also when to intensify treatment or whether it could be reduced or even suspended.

Therefore, the objective of this systematic review is to analyze the published evidence on the usefulness of ultrasound and MRI in the evaluation of treatment response in patients with gout.

Materials and Methods

We selected studies that evaluated the response to treatment of patients with gout (NSAIDs hipouricemic agents, etc., regardless of type, dose and duration of treatment) using imaging (ultrasound and/or MRI) in patients with gouty arthritis (selected regardless of the criteria for diagnosis, type and number of joints affected). We selected articles that measured correlation coefficients, sensitivity to change, changes after treatment using radiological and clinical variables (number of attacks, number of swollen joints, uric acid levels, number of tophi, disappearance of tophi, quality of life and laboratory data), variables related to safety, etc. Regarding the design of the studies, meta-analyses, systematic reviews, clinical trials, cohort and validation studies were included. Basic science articles and animal studies were excluded.

We searched the following electronic databases until February 2012: MEDLINE (from 1960), EMBASE (from 1980) and the Cochrane Library (Central). We searched both MeSH terms and free text formats. No limits were set on the publication date. In addition, we searched abstracts sent to ACR and EULAR meetings in 2010 and 2011. Finally, a manual search for articles finally included was performed. The specific search strategy is detailed in the supplementary material (see Appendix annex).

A single reviewer (VV) analyzed the articles resulting from the search as well as the detailed analysis of the items included. The first search result was filtered by title and abstract or entire article in case they were not summarized by 20 min maximum duration sessions. If in doubt, a second reviewer (EL) resolved the discrepancy. After this process, the remaining items were analyzed in detail (VV). Again, if in doubt, EL would solve it. Finally, a manual search with references selected for detailed analysis was performed. All Internet references were retrieved and placed in the EndNote software to facilitate management.

To assess the methodological quality of included studies we used: (a) for clinical trials, the Jadad scale (1–5; considering good quality studies as Jadad 3–5), and (b) for cohort studies, the Oxford quality scale.

Results

The search results are detailed in Fig. 1.

Overview of Articles Included

3 studies[9–11] were eligible for inclusion, all small prospective case series, which included a total of 36 patients with gouty arthritis (detection of uric acid crystals in the synovial fluid with polarized light microscope) and whose response to hypouricemic treatment was assessed by ultrasound. Uric acid blood concentration determinations were performed every 3 months, and one study[11] further recorded: pain by visual analog scale (VAS), global assessment of the disease by the patient (VAS), number of tender and swollen joints, excretion of uric acid, CRP and ESR. Hypouricemic treatment was adjusted based on EULAR recommendations (blood uric acid $\leq$6 mg/dL). As for the ultrasound variables analyzed, one study evaluated the change in the size of tophi,[9] another measured persistence/decrease or disappearance of the ultrasound "double contour" (deposits of uric acid crystals in the hyaline cartilage) based on serum uric acid levels[10] and, in the latter, in addition to