Portuguese recommendations for the diagnosis and management of Gout

Araújo F[1,2], Cordeiro I[3], Teixeira F[4], Rovisco J[5], Ramiro S[3,6], Mourão AF[1,6,7,8], Costa JA[4], Pimentão JB[9], Malcata A[5], Santos MJ[3,8], Branco JC[7,1]

ACTA REUMATOL PORT. 2014:39;158-171

ABSTRACT

Objective: To develop Portuguese evidence-based recommendations for the Diagnosis and Management of Gout. Methods: As part of the 3e Initiative (Evidence, Expertise and Exchange), a panel of 78 international rheumatologists developed 10 relevant clinical questions which were investigated with systematic literature reviews. MEDLINE, EMBASE, Cochrane CENTRAL and abstracts from 2010-2011 EULAR and ACR meetings were searched. Based on the evidence found in the published literature, rheumatologists from 14 countries developed national recommendations that were merged and voted into multinational recommendations. We present the Portuguese recommendations for the Diagnosis and Management of Gout which were formulated and voted by Delphi method in April 2012, in Lisbon. The level of agreement and potential impact in clinical practice was also assessed. Results: Twelve national recommendations were elaborated from 10 international and 2 national questions. These recommendations addressed the diagnosis of gout; the treatment of acute flares and urate-lowering therapy; monitoring of gout and comorbidity screening; the influence of comorbidities in drug choice; lifestyle; flare prophylaxis; management of tophi and asymptomatic hyperuricaemia; the role of urine alkalinization; and the burden of gout. The level of agreement with the recommendations ranged from 6.8 to 9.0 (mean 7.7) on a 1-10 point visual analogue scale, in which 10 stands for full agreement. Conclusion: The 12 Portuguese recommendations for the Diagnosis and Management of Gout were formulated according to the best evidence and endorsed by a panel of 42 rheumatologists, enhancing their validity and practical use in daily clinical practice.

Keywords: Recommendations; Portuguese; Gout.

1. Department of Rheumatology, Hospital de Egas Moniz, Centro Hospitalar de Lisboa Ocidental EPE
2. Institute of Microbiology, Faculdade de Medicina da Universidade de Lisboa
3. Department of Rheumatology, Hospital Garcia de Orta, Almada
4. Department of Rheumatology, Hospital Conde de Bertiandos, Ponte de Lima, Unidade Local de Saúde do Alto Minho EPE
5. Department of Rheumatology, Centro Hospitalar e Universitário de Coimbra EPE
6. Clinical Immunology & Rheumatology, AMC, Amsterdam, The Netherlands
7. CEDOC, Faculdade de Ciências Médicas da Universidade Nova de Lisboa
8. Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa
9. Rheumatology, Clínica Coração de Jesus, Lisboa

INTRODUCTION

Gout is a common inflammatory arthropathy in which monosodium urate (MSU) crystals deposit in joints, leading to self-limited arthritis and sometimes chronic deforming arthropathy and tophi[1]. Although early treatment has improved the prognosis of gout, this clinical entity is still under diagnosed and poorly managed due to patient and physician suboptimal information[2].

The 3e Initiative (Evidence, Expertise, and Exchange) is a multinational collaboration aimed at promoting evidence-based medicine through the formulation of recommendations addressing relevant clinical problems. This initiative combines the evidence obtained from systematic literature reviews (SLR) with the clinical expertise of a broad panel of international rheumatologists[3, 4]. The objective of the 2011-2012 3e Initiative was to develop practical recommendations for the Diagnosis and Management of Gout. After formulation of 10 multinational questions (and 2 additional national questions), the 12 Portuguese recommendations were proposed and voted in the national meeting in Lisbon.

METHODS

A total of 474 rheumatologists from 14 countries participated in the 3e Initiative on the Diagnosis and Management of Gout. These countries were represented by 12 scientific committees which gathered in Brussels for the kickoff meeting in June 2011. The multinational committee comprised the scientific chair (D. van der Heijde), 6 mentors (D. Aletaha, C. Bombardier, R. Buchbinder, L. Carmona, C. Edwards and R. Landewé) and 10 multinational fellows (M. Andrés, A. Kydd, J. Moi, R. Seth, F. Sivera Mascaró, M. Sriranganathan, C. Van Durme, I. van Echteld, O. Vinik and M. Wechalekar). In this first meeting, the participating rheumatologists developed and selected 10 clinically relevant questions through a modified Delphi voting process. Each of these questions was investigated with an SLR conducted by the multinational fellows. The proposals that did not reach the 10 final questions were selected by the national fellows. SLRs were undertaken and their results were, after discussion with an expert panel, integrated in the respective national recommendations.

All the SLRs were performed according to the recommendations of the Cochrane Collaboration[5]. The questions were rephrased into epidemiological terms using the PICOT (population, intervention, comparison, outcome and type of study) and, with the assistance of an experienced librarian (L. Falzon), an appropriate search strategy was outlined for each of the SLRs. The databases MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched and papers fulfilling inclusion and exclusion criteria were selected for detailed review. Abstracts from the scientific meetings of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) from 2010 and 2011 were also hand searched. All included articles were assessed for the risk of bias (ROB) using the adequate tool (Cochrane Risk of Bias tool for intervention studies[5], Hayden tool[6] for cohort studies, Newcastle--Ottawa scale for case-control studies[7], the COSMIN checklist for validation of measurement instruments[8], and the Cochrane Risk of Bias tool for diagnostic studies[9]).

The results of the SLRs were presented in the national meetings of all participating countries and each national scientific committee produced recommendations regarding the 10 multinational questions. In the closing meeting in Brussels, in June 2012, all the national recommendations were merged into 10 final recommendations through a process of discussion and modified Delphi vote[10].

The Portuguese national meeting took place in Lisbon in April 2012, with 42 Portuguese rheumatologists attending it. The national committee, including the scientific chair (J. C. Branco), the scientific committee (J. A. Costa, A. Malcata, A. F. Mourão, J. B. Pimentão, S. Ramiro and M. J. Santos) and the bibliographic fellows (F. Araújo, I. Cordeiro, J. Rovisco, F. Teixeira) presented the results of the multinational and national SLRs, which were discussed and voted into the Portuguese recommendations. The level of agreement with each statement was voted using a 10-point visual analogue scale (1 – Fully disagree; 10 – Fully agree) and impact in daily practice was also assessed (1 - this recommendation will change my practice; 2 - this recommendation is in full accordance with my practice; 3 - I do not want to apply this recommendation in my practice).

We hereby present the 12 Portuguese recommendations for the Diagnosis and Management of Gout.

RESULTS

In total, 67825 references were identified and 439 articles were reviewed (Table I). The 12 Portuguese recommendations and their respective level of evidence, grade of recommendation and level of agreement are summarized in Table II (English version) and Table III (Portuguese version). The impact of these recommendations in daily practice is found in Table IV. The level of agreement of the Portuguese participants with the final recommendations ranged from 6.8 to 9.0 (mean 7.7) on a 1-10 point visual analogue scale, in which 10 represents full agreement. The impact of the recommendations was apparent through willingness to change the clinical practice in subjects such as management of acute gout flares (recommendation 3), monitoring of gout patients (recommendation 8) management of asymptomatic hyperuricaemia (recommendation 9) and urine alkalinization (recommendation 11).

RECOMMENDATION 1

The demonstration of MSU crystals is always desirable in the case of clinical suspicion of gout. In the case of a previous good response to colchicine and/or the presence of tophi, a clinical diagnosis of gout is reasonably accurate. In the absence of visible tophi, ultrasound

TABLE I. SEARCH RESULTS FOR THE TEN MULTINATIONAL QUESTIONS (1-10) AND THE TWO NATIONAL QUESTIONS (11 AND 12)

Clinical questions	Number of identified references in the SLRs	Number of selected articles for the SLRs
1. In which circumstances can a diagnosis of gout be made on clinical grounds with or without laboratory tests or imaging and when is the identification of crystals necessary?	5572	20
2. In patients with hyperuricaemia and/or the diagnosis of gout, should we screen routinely for comorbidities and CV risk factors?	8946	65
3. What is the role of glucocorticoids, colchicine, NSAIDs, anti-IL1 and paracetamol in the management of acute gout?	1097	32
4. Which lifestyle changes (such as diet, alcohol intake, weight loss, smoking and/or exercise) are efficacious in the treatment/prevention of gout?	7534	2
5. What is the efficacy, cost efficacy and safety for urate-lowering therapy (both allopurinol but also febuxostat, peg-uricase, benzbromarone and probenecid) in the treatment of gout? Which sequence of uric acid lowering drugs or combinations of should be recommended?	5559	109
6. When introducing ULT, what is the best treatment to prevent an acute.attack, and for how long should it be continued? When is the optimum time to start ULT after an acute attack of gout?	8365	4
7. How do common comorbidities (such as metabolic syndrome, CV, GI, and renal disease) influence the choice of gout specific drugs (such as colchicine, allopurinol and other ULT) in acute gout flare, chronic gout and in prophylaxis of acute flare?	5741	9
8. What should be the treatment target and how should patients with gout be followed (with which measures (e.g patient reported outcome, clinical, biochemical, and/or imaging))?	4584	54
9. How should tophi be managed?	3206	72
10. Can we prevent gouty arthritis, renal disease and CV events by lowering serum uric acid levels in patients with asymptomatic hyperuricaemia? If yes, what should be the target levels?	1694	3
11. What is the efficacy and safety of urine alkalinization in patients with gout or uric acid lithiasis?	7103	5
12. What is the overall burden of gout and how is it measured across trials?	9521	64

CV – cardiovascular, GI – gastrintestinal, IL – interleukin, NSAID – non-steroidal anti-inflammatory drug, SLR – systematic literature review, ULT – urate lowering therapy.

or computerized tomography (CT) scan may be useful in the diagnosis.

Nineteen studies (corresponding to 20 papers)[11-30] concerning the diagnostic accuracy of gout were identified. However, only 4 studies (corresponding to 5 articles)[15-17, 19, 21] used MSU crystal identification in synovial fluid as a reference standard to which comparison was performed. The two clinical features that showed good diagnostic performance were previous good response to colchicine during an acute inflammatory attack (positive likelihood ratio, LR+, of 4.33) and the presence of tophi in physical examination (LR+ of 15.56 in one study[21] and 30.88 in another[15]). However, response of acute arthritis to colchicine was not useful to differentiate types of crystal arthritis, namely gout and acute calcium pyrophosphate arthritis. Amongst the evaluated laboratory features, the absence of hyperuricaemia showed a marked negative LR

TABLE II. TWELVE PORTUGUESE RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF GOUT (ENGLISH VERSION), WITH RESPECTIVE LEVEL OF EVIDENCE (OXFORD LEVELS OF EVIDENCE), GRADE OF RECOMMENDATION AND LEVEL OF AGREEMENT (VOTED ON A SCALE FROM 1 TO 10 IN WHICH 1 - I FULLY DISAGREE AND 10 - I FULLY AGREE)

Recommendation	Level of evidence	Grade of recommendation	Agreement, mean (SD)
1. The demonstration of monosodium urate crystals is always desirable in the case of clinical suspicion of gout. In the case of a previous good response to colchicine and/or the presence of tophi, a clinical diagnosis of gout is reasonably accurate*. In the absence of visible tophi, ultrasound or CT may be useful in the diagnosis**.	*2b **2b	*D **B	7.7 (1.6)
2. In the presence of hyperuricaemia and/or gout, diabetes mellitus, hypertension and dyslipidemia should be screened. It is further recommended to evaluate renal function. There should be given special attention to the suspicion and diagnosis of coronary disease.	2c	C	8.7 (1.6)
3. In the management of acute gout, low dose of oral colchicine* or NSAIDs** are recommended. In case of inefficacy, contraindication or intolerance, consider the use of systemic glucocorticoids*** or IL-1 inhibitors****. Despite the lack of evidence, intra-articular glucocorticoids may be used*****.	*1b- **1a- ***1a- ****2b *****4	*D **D ***D ****D *****D	7.0 (2.2)
4. A diet low in purines, alcohol, sugary drinks and fructose is recommended in the prevention/treatment of gout. There may be a benefit with weight control.	5	D	8.2 (1.3)
5. Allopurinol* is recommended as the first line of urate-lowering treatment, due to the lack of studies on treatment strategies and the lack of a therapeutic alternative in Portugal. Febuxostat**, PEG-uricase***, benzbromarone**** and probenecid**** are also efficacious in lowering urate levels. The safety profile is favorable, except for pegloticase which appears to be associated with an increased number of hypersensitivity reactions***.	*2b **2b ***2b ****2b	*C **C ***C ****C	8.1 (1.2)
6. When starting ULT, prophylaxis with colchicine at a minimum dose of 1mg/day for at least 6 months should be done*. In case of intolerance or contraindication to the use of colchicine, consider other alternatives, including NSAIDs** or low dose corticosteroids***. The introduction of ULT should be delayed until complete resolution of the gouty crisis****.	*1b **5 ***5 ****5	*B **D ***D ****D	9.0 (1.0)
7. In patients with gout and concomitant mild to moderate CKD, allopurinol* or febuxostat** (when available in Portugal) should preferably be used to reduce uric acid levels/prevent further gouty attacks. There is no evidence regarding the influence of other comorbidities in the treatment of different phases of the disease, and therefore the opinion of the clinician prevails.	*4 **2b	*D **B	8.5 (1.3)
8. The therapeutic target should be a reduction in serum uric acid, with the objective of maintaining levels of < 6 mg/dL (0.36mmol/L)*. For patients with tophaceous gout, the aim should be to achieve levels of < 5mg/dL (0.30mmol/L)**. The follow-up of the patient should be individualized. In addition to the monitorization of uric acid and the clinical assessment, other assessment tools (eg HAQ, SF-36) may be used***.	*2b **2b ***5	*C **B ***D	7.0 (2.3)

continues on the next page

TABLE II. CONTINUATION

Recommendation	Level of evidence	Grade of recommendation	Agreement, mean (SD)
9. Tophi are adequately managed through an efficacious reduction of the serum uric acid. There is no specific drug therapy. In particular cases, surgical removal of tophi may be recommended.	2b	B	7.6 (1.6)
10. The pharmacological treatment of asymptomatic hyperuricemia is not recommended*. In subjects with serum uric acid > = 9 mg/dL, pharmacological treatment should be considered after an individual assessment of risk/benefit ratio, particularly in the prevention of gout**.	*2b **5	*D **D	6.8 (1.5)
11. In patients with uric acid lithiasis, urine alkalinization may be useful in the elimination of stones.	1b	B	8.0 (1.3)
12. Gout is a common disease at middle-age and its impact should not be overlooked. The measures recommended by OMERACT should be included in the clinical investigation of gout, in order to quantify its impact.	5	D	7.6 (2.0)

CKD – chronic kidney disease, CT – computed tomography, HAQ: health assessment questionnaire, IL – interleukin, OMERACT – outcome measures in rheumatology clinical trials, NSAID – non-steroidal anti-inflammatory drug, SF: short form, ULT – urate lowering therapy

(LR-), independently of the defined cut-off value[15, 21]. Concerning imaging features, the presence of the double contour sign in ultrasound (US) and the presence of urate deposits in dual-energy computed tomography (DECT) showed a high LR+ (13.63 and 9.5, respectively)[17, 19]. The DECT is also coupled with a very low negative likelihood ratio, increasing its diagnostic performance, but may be limited by availability, cost, and the need for trained personnel and specific equipment. There was consensus among experts that MSU crystal demonstration is always desirable to confirm the diagnosis of gout. However, in the absence of crystal identification, the previously mentioned clinical and imaging features allow a confident diagnosis of gout.

RECOMMENDATION 2

In the presence of hyperuricaemia and/or gout, diabetes mellitus, hypertension and dyslipidaemia should be screened. It is further recommended to evaluate renal function. There should be given special attention to the suspicion and diagnosis of coronary heart disease.

An increased risk of developing diabetes[31-35] and hypertension[34, 36-40] was found in patients with hyperuricaemia (hazard ratio, HR, ≈2), but no prospective studies were available in patients with gout. Gout patients had a slight increase in both coronary heart disease (CHD) incidence and mortality[41-46], while hyperuricaemia only seemed to increase the risk of CHD-related mortality, especially in women[47-51]. No relationship was found between hyperuricaemia, gout and stroke. Although no prospective studies on dyslipidaemia and metabolic syndrome were found, there was consensus among Portuguese experts that screening for these conditions should be performed in patients with hyperuricaemia and/or gout. Hyperuricaemia increased the risk of progression to end-stage renal disease (ESRD). Although gout was not found to be an independent predictor for ESRD, an increased risk of death due to chronic kidney disease was found in gout patients (HR ≈ 4 for both)[46, 52, 53].

RECOMMENDATION 3

In the management of acute gout, low dose of oral colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) are recommended. In case of inefficacy, contraindication or intolerance, consider the use of systemic glucocorticoids or IL-1 inhibitors. Despite the lack of evidence, intra-articular glucocorticoids may be used.

Two high quality trials revealed superiority of colchicine when compared to placebo in the treatment of acute gout, one of them showing similar efficacy between low dose (total of 1.8 mg in 24 hours) and high dose colchicine with a significant better safety profile in the low dose regimen[54, 55]. Only one trial assessed the efficacy of NSAIDs against placebo, finding no diffe-

TABLE III. TWELVE PORTUGUESE RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF GOUT (PORTUGUESE VERSION), WITH RESPECTIVE LEVEL OF EVIDENCE (OXFORD LEVELS OF EVIDENCE), GRADE OF RECOMMENDATION AND LEVEL OF AGREEMENT (VOTED ON A SCALE FROM 1 TO 10 IN WHICH 1 - I FULLY DISAGREE AND 10 - I FULLY AGREE)

Recomendação	Nível de evidência	Grau de recomendação	Concordância, média (DP)
1. A demonstração de cristais de monourato de sódio é sempre desejável na suspeita clínica de gota. Perante boa resposta prévia à terapêutica com colchicina e/ou presença de tofos, o diagnóstico clínico de gota é razoavelmente preciso*. Na ausência de tofos, a ecografia ou a TC podem ter utilidade diagnóstica**.	*2b **2b	*D **B	7.7 (1.6)
2. Na presença de hiperuricémia e/ou gota, a diabetes mellitus, a hipertensão arterial e a dislipidémia devem ser rastreados. Recomenda-se ainda a avaliação da função renal. Deve existir um elevado grau de suspeita diagnóstica de doença coronária.	2c	C	8.7 (1.6)
3. No tratamento da crise aguda de gota recomenda-se o uso de doses baixas de colchicina* ou AINEs** orais. Perante ineficácia, contra-indicação ou intolerância, deve ser ponderado o uso de glicocorticóides sistémicos*** ou inibidores da IL-1****. Apesar da ausência de evidência, os glicocorticóides intra-articulares poderão ser utilizados*****.	*1b- **1a- ***1a- ****2b *****4	*D **D ***D ****D *****D	7.0 (2.2)
4. Uma dieta pobre em purinas, álcool, bebidas açucaradas e frutose é recomendada na prevenção/tratamento da gota. Pode existir benefício com o controlo ponderal.	5	D	8.2 (1.3)
5. Alopurinol* é o tratamento hipouricemiante de primeira linha pela ausência de alternativas em Portugal e de estudos sobre estratégias terapêuticas. Febuxostato**, PEG-uricase***, benzbromarona**** e probenecide**** são também eficazes como hipouricemiantes. Os perfis de segurança são favoráveis, excepto para a pegloticase, que parece estar associada a um número aumentado de reacções de hipersensibilidade***.	*2b **2b ***2b ****2b	*C **C ***C ****C	8.1 (1.2)
6. Ao iniciar terapêutica hipouricemiante, deve realizar-se profilaxia com colchicina numa dose mínima de 1 mg/dia pelo menos durante 6 meses*. Em caso de intolerância ou contra-indicação ao uso de colchicina, alternativas como AINEs** ou corticosteróides*** em dose baixa devem ser consideradas. O início de terapêutica hipouricemiante deve ser protelada até resolução completa da crise gotosa aguda****.	*1b **5 ***5 ****5	*B **D ***D ****D	9.0 (1.0)
7. Em doentes com gota e doença renal crónica ligeira a moderada concomitante, alopurinol* ou febuxostato** (quando disponível em Portugal) devem ser usados preferencialmente para reduzir a uricémia/ /prevenção de novos ataques de gota. Não existe evidência relativamente à influência de outras comorbilidades no tratamento de diferentes fases da doença, prevalecendo assim a opinião do médico assistente.	*4 **2b	*D **B	8.5 (1.3)
8. O alvo terapêutico deverá ser a redução da uricémia com o objectivo de manter valores < 6 mg/dL (0.36mmol/L)*. Nos doentes com gota tofácea, o objectivo deverá ser uricémia < 5mg/dL (0.30mmol/L)**. O seguimento do doente deverá ser individualizado. Para além da monitorização clínica e da uricémia, outros instrumentos (como o HAQ ou o SF-36) podem ser utilizados***.	*2b **2b ***5	*C **B ***D	7.0 (2.3)

continues on the next page

TABLE III. CONTINUATION

Recomendação	Nível de evidência	Grau de recomendação	Concordância, média (DP)
9. Os tofos são adequadamente tratados através da redução eficaz da uricémia. Não existe nenhum fármaco específico para o tratamento dos tofos. Em casos particulares, a sua ressecção cirúrgica poderá estar indicada.	2b	B	7.6 (1.6)
10. O tratamento farmacológico da hiperuricémia assintomática não está recomendado*. Em indivíduos com uricémia ≥ 9 mg/dL, o tratamento farmacológico deve ser considerado após avaliação individual do risco/benefício, particularmente na prevenção do surgimento de gota**.	*2b **5	*D **D	6.8 (1.5)
11. Em doentes com litíase renal por ácido úrico, a alcalinização da urina pode ser útil na eliminação dos cálculos.	1b	B	8.0 (1.3)
12. A gota é uma doença frequente nos adultos de meia idade e o seu impacto não deve ser negligenciado. Os domínios de medição recomendados pelo OMERACT devem ser incluídos nos ensaios clínicos de gota, de forma a quantificar o seu impacto.	5	D	7.6 (2.0)

AINE – anti-inflamatório não esteróide, HAQ: health assessment questionnaire, IL – interleucina, OMERACT – outcome measures in rheumatology clinical trials, SF: short form, TC – tomografia computorizada.

rence in pain, swelling and erythema at 24 hours[56]. This was, however, a low quality trial. Seventeen trials compared different NSAIDs, finding no significant difference in efficacy[57-73]. No placebo-controlled trials assessing the use of systemic glucocorticoids in gout were found, but when compared to NSAIDs they seem to be as effective and have a better safety profile[74-78]. Canakinumab, an IL-1 inhibitor, was more effective in the dosage of 150 mg than a single intramuscular injection of triamcinolone acetonide 40 mg, with a similar safety profile, in only one trial with a moderate ROB[78]. Albeit not yet available in Portugal, this drug was recently approved by the European Medicines Agency for the treatment of gout attacks when colchicine, NSAIDs or systemic glucocorticoids were ineffective, contraindicated or not tolerated[135]. Although no trials were found concerning the use of intra-articular long-acting glucocorticoids during an acute attack of gout, experts considered it a valid therapeutic option based in their clinical expertise.

RECOMMENDATION 4

A diet low in purines, alcohol, sugary drinks and fructose is recommended in the prevention/treatment of gout. There may be a benefit with weight control.

Although the promotion of a healthy lifestyle is a common practice in the non-pharmacological management of gout, only two trials assessing these interventions were found. In the first trial, there was no benefit in the frequency of gout flares with the use of enriched skim milk powder compared with standard skimmed milk or lactose powder[79]. In the second trial, at a high ROB, the use of topical ice relieved pain in patients with acute gout[134]. Many trials assessing the effect of different lifestyle interventions in the level of serum uric acid (sUA) were identified, however they were all either low quality or underpowered. The experts agreed that general healthy lifestyle principles such as dietary restriction in purines, alcohol, sugary drinks and fructose should be advisable to all individuals, but especially to gout patients. This statement was based on data from previously known epidemiological studies of gout and their own clinical experience.

RECOMMENDATION 5

Allopurinol is recommended as the first line of urate-lowering treatment (ULT), due to the lack of studies on treatment strategies and the current lack of a therapeutic alternative in Portugal. Febuxostat, PEG-uricase, benzbromarone and probenecid are also efficacious in lowering urate levels. The safety profile is favourable, except for pegloticase which appears to be associated with an increased number of hypersensitivity reactions.

Since no studies addressing a possible sequence of ULT were found and considering the current lack of the-

TABLE IV. IMPACT OF THE RECOMMENDATIONS ON THE PRACTICE OF PORTUGUESE RHEUMATOLOGISTS

Recommendation (number and topic)	This recommendation will change my practice, %	This recommendation is in full accordance with my practice, %	I do not want to apply this recommendation in my practice, %
1. Diagnosis	12.1	87.9	0
2. Comorbidity screening	23.5	73.5	2.9
3. Acute gout	33.3	51.5	15.2
4. Lifestyle	11.1	88.9	0
5. Urate lowering therapy	2.9	94.1	2.9
6. Flare prophylaxis	15.8	84.2	0
7. Effect of comorbidities on drug choices	21.6	78.4	0
8. Monitoring	51.7	27.6	20.7
9. Tophi	11.8	88.2	0
10. Asymptomatic hyperuricaemia	32.1	60.7	7.1
11. Urine alkalinization	41.9	45.2	12.9
12. Burden of gout	NA	NA	NA

NA- not applicable.

rapeutic alternatives in Portugal, the experts recommended the use of allopurinol as first line therapy.

Four trials of allopurinol 300 mg/day showed superiority to placebo and similar efficacy to febuxostat 40 mg/day in achieving sUA < 6 mg/dL. Febuxostat 80--240 mg/day was more effective than allopurinol 300 mg/day, but this dosage of allopurinol may be considered suboptimal. When initiating ULT, the association of allopurinol 300 mg/day and colchicine caused no more acute gout flares than placebo or febuxostat 80 mg/day, also associated with colchicine. It caused, however, significantly less flares when compared to the association of febuxostat 120-240 mg/day and colchicine[80-84]. Allopurinol and febuxostat had a similar safety profile[80-84]. Step-up therapy with allopurinol 300-600 mg or benzbromarone 100-200 mg was equally effective in lowering sUA levels[83]. In patients who have failed to reach target sUA levels, benzbromarone is more effective and well tolerated than probenecid[85]. Pegloticase (PEG-uricase) showed significant efficacy as ULT but there was increased occurrence of acute flares, infusion reactions and withdrawals due to adverse events (AE)[86].

RECOMMENDATION 6

When starting ULT, prophylaxis with colchicine at a minimum dose of 1mg/day for at least 6 months should be undertaken. In case of intolerance or contraindication to the use of colchicine, consider other alternatives, including NSAIDs or low dose systemic corticosteroids. The introduction of ULT should be delayed until complete resolution of the gouty crisis.

Good quality evidence on the efficacy of colchicine in preventing acute gout flares when starting ULT was found in one trial that used 1.2 mg/day for an average of 5 months but with greater benefit for patients taking it for 6 months[87]. Two other high ROB trials were found, the first confirming the efficacy of colchicine[88] and the second showing lower recurrence of gout flares when prophylatic treatment lasted for at least 7 months[89]. No significant difference between side effects of colchicine and placebo was found. Trials addressing other prophylatic treatments were not found. However, there was consensus among experts that NSAIDs and low dose systemic glucocorticoids should be considered in the setting of intolerance or contraindication to colchicine. There was also no evidence concerning the optimum time to start ULT treatment after an acute attack of gout, but experts agreed that introduction of these drugs should be withheld until complete resolution of the attack.

RECOMMENDATION 7

In patients with gout and concomitant mild to moderate chronic kidney disease (CKD), allopurinol or febuxostat (when available in Portugal) should preferably be used to reduce uric acid levels/prevent further gouty attacks. There is no evidence regarding the influence of other comorbidities in the treatment of dif-

ferent phases of the disease, and therefore the opinion of the clinician prevails.

Two trials (one at low and another at unclear ROB) assessed gout therapy in patients with mild to moderate CKD (creatinine clearance > 30 ml/min). In both trials, all doses of febuxostat (specially ≥ 80 mg/day) were more effective than allopurinol adjusted to renal function (100-200 mg/day), with similar AE[82, 84]. Other trials, all of low quality, addressed the renoprotective effect of allopurinol and benzbromarone[90, 91]; the efficacy and safety of rasburicase and benzbromarone in CKD[91-93]; and allopurinol dose escalation in patients with renal impairment[91, 92]. There was consensus among experts that patients with gout and CKD should be treated with allopurinol adjusted to renal function or febuxostat, when available in Portugal. Due to lack of evidence, the choice of gout therapy in patients with other comorbidities should be based on individual clinical judgment.

RECOMMENDATION 8

The therapeutic target should be a reduction in serum uric acid, with the objective of maintaining levels of < 6 mg/dL (0.36mmol/L). For patients with tophaceous gout, the aim should be to achieve levels of < 5mg/dL (0.30mmol/L). The follow-up of the patient should be individualized. In addition to the monitorization of uric acid and the clinical assessment, other assessment tools (eg, Health Assessment Questionnaire, SF-36) may be used.

Experts agreed that the reduction in sUA should be the main target of gout treatment based on low to moderate quality trials in which this reduction was associated with fewer gout flares[96-101], tophus regression[102,103] and MSU crystal clearance from synovial fluid[104-106]. Although different cut-off levels were found, there was consensus that sUA should be maintained below 6 mg/dL (0.36 mmol/L) since this was the most frequently used value in clinical trials. Two observational studies showed that lower target sUA levels were associated with faster tophi regression[102,103]. Many instruments were tested for monitoring gout patients. Besides sUA levels, SF-36 (physical component)[107,108] and the Health Assessment Questionnaire[107,109] showed the adequate clinimetric properties, experts agreed that the follow-up of these patients should be performed on an individual basis.

RECOMMENDATION 9

Tophi are adequately managed through an efficacious reduction in sUA. There is no specific drug therapy. In particular cases, surgical removal of tophi may be recommended.

Very few studies focused on specific pharmacological management of tophi. Low to moderate quality trials showed that pegloticase (PEG-uricase) 8 mg biweekly[86], febuxostat 120 mg/day[82] and the combination of allopurinol 200 mg/day and benzbromarone 50 mg/day[102] improved tophi size and number, sometimes with complete resolution. The experts considered this improvement to be related to successful lowering of sUA and not to specific drugs. Evidence to support surgical intervention for tophi comes only from case series/reports in which patients suffering from complications (like nerve compression or infection) showed improved function and pain reduction following surgery.

RECOMMENDATION 10

The pharmacological treatment of asymptomatic hyperuricaemia is not recommended. In subjects with sUA ≥ 9 mg/dL, pharmacological treatment should be considered after an individual assessment of risk/benefit ratio, particularly in the prevention of gout.

No evidence was found supporting the treatment of asymptomatic hyperuricaemia. Only 3 trials at a high ROB assessed variation of renal parameters with allopurinol treatment in patients with hyperuricaemia with and without CKD, but found no significant difference when compared to placebo[110-112]. No trials appraising gout or cardiovascular prevention in asymptomatic hyperuricaemia were retrieved. Based on the large observational Framingham (1967) and Normative Aging (1987) studies, which demonstrated increased risk of gout in patients with hyperuricaemia (specially with sUA ≥ 9 mg/dL), there was moderate consensus among experts that subjects exceeding this level should be considered for ULT in order to prevent the onset of gout.

RECOMMENDATION 11

In patients with uric acid lithiasis, urine alkalinization may be useful in the elimination of stones.

Three good to moderate quality trials addressing the use of urine alkalinization were found, although none referred to patients with gout. One trial demonstrated the efficacy of potassium citrate in the elimination of uric acid stones, which seemed to be enhanced in patients taking concurrent tamsulosin[113]. Although statistical significance was reached, this study was conducted on patients with nephrolithiasis rather than

gouty patients. Two other trials showed significant increase in urinary pH and uric acid clearance with potassium citrate, one in patients with nephrolithiasis[114], the other in patients with hyperuricaemia[115]. Taking this evidence into account, experts considered that urine alkalinization could be efficacious and safe in the elimination of uric acid stones, albeit the lack of studies in patients with gout.

RECOMMENDATION 12

Gout is a common disease at middle-age and its impact should not be overlooked. The measures recommended by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) should be included in the clinical investigation of gout, in order to quantify its impact.

Sixty-four trials of gout were reviewed and the disease impact was extrapolated from baseline characteristics of patients with gout included in the trials[35,54-74,76-78,80-91,116-133]. The chosen methodology has some limitations in the assessment of the burden of the disease based on patients included in RCTs. Nevertheless, it seemed the most feasible option to still obtain relevant information, as epidemiologic studies are scarce and very heterogeneous in what they report, not allowing for the assessment of the burden of the disease. Trials were also somewhat heterogeneous in terms of the variables assessed and the measures used, rendering comparisons difficult. Gout was associated predominantly with monoarticular (72% of the patients) acute flares of high intensity-pain (mean visual analogue scale 79/100 mm), with variable duration and a high recurrence rate (mean of 4.4 flares in the previous year). Tophi were present in one fifth of the patients with chronic gout. Disability, quality of life and patient/physician global assessment were seldom reported. These would be characteristics that would enable a better understanding of the burden of the disease, if they had been reported. However, despite being OMERACT recommended outcome measures, they were not reported in the majority of the trials (neither as outcome, nor as baseline characteristic). Experts agreed that gout is a common disease that affects subjects in their working-age, carrying a significant burden that should be assessed in clinical trials through the outcome measures proposed by the OMERACT initiative.

DISCUSSION

The 12 Portuguese recommendations for the diagnosis and management of gout were presented. These recommendations were elaborated and voted by Portuguese experts as part of the 3e Initiative and were based in the best available evidence from 12 different SLRs.

Although gout has been recognized as a serious and potentially debilitating disease and several international recommendations were published, gout management is still not optimal. These evidence-based recommendations were aimed at providing a current quality resource for the approach and management of these patients. Despite the lack of supporting evidence in certain matters (for instance, lifestyle, flare prophylaxis or the effect of comorbidities in drug choices), the majority of the recommendations was based on the results of RCTs and good quality cohort studies. Among Portuguese rheumatologists, there was a moderate-to-high level of agreement with the issued recommendations and also an evident willingness to modify their clinical practice according to these orientations, particularly those regarding the burden of gout, urine alkalinization, monitoring of gout patients or management of acute gout.

CONCLUSION

In summary, the 12 Portuguese Recommendations for the Diagnosis and Management of Gout were developed with the ultimate purpose of improving patient care, integrating both scientific data from trials and the opinion of clinical experts.

CORRESPONDENCE TO

Filipe Araújo
Rheumatology Department, Hospital de Egas Moniz,
CHLO EPE
Rua da Junqueira, 126
1349-019 Lisboa, Portugal
E-mail: flipar@msn.com

REFERENCES

1. McLean L and Becker M. Etiology and pathogenesis of gout. In: Hochberg MC, Silman AJ, et al. Rheumatology. Philadelphia: Elsevier, 2011:1841-1858.
2. Doherty M, Jansen TL, Nuki G, et al. Gout: Why is this curable disease so seldom cured? Ann Rheum Dis 2012;71:1765--1770.
3. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3e Initiative. Ann Rheum Dis 2009;68:1086-1093.
4. Silva I, Mourão F, Ramiro S, et al. Recomendações portuguesas

para o tratamento e controlo farmacológico da dor nas artropatias inflamatórias. Acta Reumatol Port 2012;37:160-174.
5. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Accessed November 2011.
6. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427-437.
7. Newcastle-Ottawa quality assessment scale: case control studies. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (Accessed at February 2012)
8. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res 2010;19:539-549.
9. Reitsma J, Rutjes A, Whiting P, Vlassov V, Leeflang M, Deeks J. Chapter 9: Assessing methodological quality. In: Deeks J, Bossuyt P, Gatsonis C, eds. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Version 100): The Cochrane Collaboration; 2009.
10. Sivera F, Andrès M, Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis 2013;0:1-8. Doi:10.1136/annrheumdis-2013--203325.
11. Artmann A, Ratzenbock M, Noszian I, Trieb K. Dual energy CT – a new perspective in the diagnosis of gout. Rofo 2010;182: 261-266.
12. Choi HK, Al-Arfaj AM, Eftekhari A et al. Dual energy computed tomography in tophaceous gout. Ann Rheum Dis 2009;68:1609-1612.
13. Filippucci E, Gutierrez M, Georgescu D et al. Hyaline cartilage involvement in patients with gout and calcium pyrophosphate deposition disease. An ultrasound study. Osteoarthritis Cartilage 2009;17:178-181.
14. Filippucci E, Scire CA, Delle Sedie A et al. Ultrasound imaging for the rheumatologist XXV. Sonographic assessment of the knee in patients with gout and calcium pyrophosphate deposition disease. Clin Exp Rheumatol 2010;28:2-5.
15. Janssens HJEM, Fransen J, van de Lisdonk EH et al. A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis. Arch Intern Med 2010;170:1120-1126.
16. Janssens HJEM, Janssen M, van de Lisdonk EH et al. Limited validity of the American College of Rheumatology criteria for classifying patients with gout in primary care. Ann Rheum Dis 2010;69:1255-1256
17. Glazebrook KN, Guimaraes LS, Murthy NS et al. Identification of intraarticular and periarticular uric acid crystals with dual-energy CT:initial evaluation. Radiology 2011;261:516-524
18. Howard RG, Pillinger MH, Gyftopoulos S et al. Reproducibility of musculoskeletal ultrasound for determining monosodium urate deposition: concordance between readers. Arthritis Care Res 2016311456-62.
19. Lai KL, Chiu YM. Role of ultrasonography in diagnosing gouty arthritis. J Med Ultrasound 2011;19:7-13
20. Lopes FPPL, de Azevedo MNL, Marchion E et al. Use of 99mTc-anti-CD3 scintigraphy in the differential diagnosis of rheumatic diseases. Rheumatology 2010;49:933-939.
21. Malik A, Schumacher HR, Dinnella JE, Clayburne GM. Clinical diagnostic criteria for gout: comparison with the gold standard of synovial fluid crystal analysis. J Clin Rheumatol 2009;15:22-24.
22. Nalbant S, Corominas H, Hsu B et al. Ultrasonography for assessment of subcutaneous nodules. J Rheumatol 2003;30:1191--1195.
23. Rettenbacher T, Ennemoser S, Weirich H e al. Diagnostic imaging of gout:comparison of highresolution US versus conventional X-rays. Eur Radiol 2008;18:621-630.
24. Rigby AS, Wood PHN. Serum uric acid levels and gout: what does this herald for the population?. Clin Exp Rheumatol 1994;12:395-400.
25. Thiele RG, Sclesinger N . Diagnosis of gout by utlrasound. Rheumatology 2007;46:1116-1121.
26. Trentham DE, Hamm RL, Masi AT. Wrist arthrography: review and comparison of normals, rheumatoid arthritis and gout patients . Semin Arthritis Rheum 1975;5:105-120.
27. Vazquez-Mellado J, Hernandez-Cuevas CB, Alvarez-Hernandez E et al. The diagnostic value of the proposal for clinical gout diagnosis (CGD). Clin Rheumatol 2011 [epub].
28. Wallace SL, Bernstein D, Diamond H. Diagnostic value of the colchicine therapeutic trial. JAMA 1967;199:525-528.
29. Wallace SL, Robinson H, Masi AT et al. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895-900.
30. Wright SA, Filippucci E, McVeigh C et al. High-resolution ultrasonography of the first metatarsal phalangeal joint in gout:a controlled study. Ann Rheum Dis 2007;66:859-864.
31. Bhole V, Choi WJW, et al. Serum uric acid levels and the risk of type 2 diabetes: a prospective study. Am J Med 2010;123:957--961.
32. Dehghan A, M van Hoek, et al. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care 2008;31:361-362.
33. Meisinger C, B Thorand, et al. Sex differences in risk factors for incident type 2 diabetes mellitus: The MONICA Augsburg Cohort study. Arch Intern Med 2002;162:82-89.
34. Taniguchi Y, Hayashi T, et al. Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. J Hypertens 2001;19(7): 1209-1215.
35. Wang T, Bi Y, et al. Serum uric acid associates with the incidence of type 2 diabetes in a prospective cohort of middle aged and elderly Chinese. Endocrine 2011; 40: 109-116.
36. Imazu M, Yamamoto H, et al. Hyperinsulinemia for the development of hypertension: Data from the Hawaii Los Angeles Hiroshima study. Hypertens Res 2001;24: 531-536.
37. Krishnan E, Baker JF, Furst DE, et al. Gout and the risk of acute myocardial infarction. Arthrits Rheum 2006;54:2688-2696.
38. Nakanishi N, Okamoto M, et al. Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. Eur J Epidemiol 2003;18:523-530.
39. Shankar A, Klein R, et al. The association between serum uric acid level and long term incidence of hypertension: Population based cohort study. J Hum Hypertens 2006; 20:937-945.
40. Zhang W, Sun K, et al. Plasma uric acid and hypertension in a Chinese community: Prospective study and meta analysis. Clin Chem 2009;55:2026-2034.
41. Abbott RD, Brand FN, et al. Gout and coronary heart disease: The Framingham Study. J Clin Epidemiol 1998;41:237-242.
42. Choi HK and Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation 2007;116: 894-900.

43. De Vera MA, Rahman MM, et al. Independent impact of gout on the risk of acute myocardial infarction among elderly women: a population based study. Ann Rheum Dis 2010;69:1162-1164.
44. Kuo CF, Yu KH, et al. Gout is an independent risk factor for acute myocardila infarction in young and low risk patients: a nationwide population study. 2011.
45. Krishnan E., Svendsen K, et al. Longterm cardiovascular mortality among middle aged men with gout. Arch Intern Med 2008;168:1104-1110.
46. Teng GG, Ang LW, et al. Mortality due to coronary heart disease and kidney disease among middle aged and elderly men and women with gout in the Singaopore Chinese health study. Ann Rheum Dis 2011;doi: 10.1136/ard.2011.
47. Aboa Eboule AC, De Smet P, et al. Relation between uricemia and total, cardiovascular and coronary mortality in both genders of nonselected sample of the Belgium population. Rev Epidemiol et Sante Publique 2001;49:531-539.
48. Baibas N, Trichopoulou A, et al. Residence in mountainous compared with lowland areas in relation to total and coronary mortality. A study in rural Greece. J Epidemiol Community Health 2005;59:274-278.
49. Fang J and Alderman MH. Serum uric acid and cardiovascular mortality: The NHANES I Epidemiologic Followup Study, 1971-1992. JAMA 2000;283:2404-2410.
50. Freedman D S, Williamson DF, et al.Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow up Study. Am J Epidemiol 1995;141:637-644.
51. Gerber Y, Tanne D, et al. Serum uric acid and longterm mortality from stroke, coronary heart disease and all causes. European Journal of Cardiovascular Prevention & Rehabilitation 2006;13:193-198.
52. Iseki K, Ikemiya Y, et al. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. Am J Kidney Dis 2004;44:642-650.
53. Hsu CY, Iribarren C, et al. Risk factors for end-stage renal disease: 25 year follow-up. Arch Int Med 2009;169:342-350.
54. Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks PM, Jones M. Does colchicine work? The results of the first controlled study in acute gout. Aust N Z J Med 1987;17:301-304.
55. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum 2010;62:1060-1068.
56. Garcia de la Torre I. A comparative, double-blind, parallel study with tenoxicam vs placebo in acute gouty arthritis. Investigacion Medica Internacional 1987;14:92-97.
57. Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. J Rheumatol 1988;15:1422-1426.
58. Butler RC, Goddard DH, Higgens CS, et al. Double-blind trial of flurbiprofen and phenylbutazone in acute gouty arthritis. Br J Clin Pharmacol 1985;20:511-513.
59. Cheng T-T, Lai H-M, Chiu C-K, Chem Y-C. A single-blind, randomized, controlled trial to assess the efficacy and tolerability of rofecoxib, diclofenac sodium, and meloxicam in patients with acute gouty arthritis. Clin Ther 2004;26:399-406.
60. Douglas G, Thompson M. A comparison of phenylbutazone and flufenamic acid in the treatment of acute gout. Ann Phys Med 1970;10:275-280.
61. Eberl R, Dunky A. Meclofenamate sodium in the treatment of acute gout. Results of a double-blind study. Arzneimittelforschung 1983;33(4A):641-643.
62. Lederman R. A double-blind comparison of Etodolac (Lodine) and high doses of naproxen in the treatment of acute gout. Advances in Therapy 1990;7(6):344-354.
63. Lomen PL, Turner LF, Lamborn KR, Winbald MA, Sack RL, Brinn EL. Flurbiprofen in the treatment of acute gout. A comparison with indomethacin. Am J Med 1986;80(3A):134-139.
64. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout. Curr Med Res Opin 1991;12:423-429.
65. Rubin BR, Burton R, Navarra S, et al. Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. Arthritis & Rheumatism 2004;50:598-606.
66. Schumacher HR Jr, Boice JA, Daikh DI, et al. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. BMJ 2002;324:1488-1492.
67. Shrestha M, Morgan DL, Moreden JM, Singh R, Nelson M, Hayes JE. Randomized double-blind comparison of the analgesic efficacy of intramuscular ketorolac and oral indomethacin in the treatment of acute gouty arthritis. Ann Emerg Med 1995; 26:682-586.
68. Smyth CJ, Percy JS. Comparison of indomethacin and phenylbutazone in acute gout. Ann Rheum Dis 1973;32:351-353.
69. Sturge RA, Scott JT, Hamilton EB, et al. Multicentre trial of naproxen and phenylbutazone in acute gout. Ann Rheum Dis 1977;36:80-82.
70. Tumrasvin T, Deesomchok U. Piroxicam in treatment of acute gout high dose versus low dose. J Med Assoc Thai 1985;68(3): 111-116.
71. Valdes EF. Use of tenoxicam in patients with acute gouty arthritis. Eur J Rheumatol Inflamm 1987;9:133-136.
72. Weiner GI, White SR, Weitzner RI, Rubinstein HM. Double-blind study of fenoprofen versus phenylbutazone in acute gouty arthritis. Arthritis Rheum 1979;22:425-426.
73. Willburger RE, Mysler E, Derbot J, et al. Lumiracoxib 400 mg once daily is comparable to indomethacin 50 mg three times daily for the treatment of acute flares of gout. Rheumatology 2007;46(7):1126-1132.
74. Axelrod D, Preston S. Comparison of parenteral adrenocorticotropic hormone with oral indomethacin in the treatment of acute gout. Arthritis Rheum 1988;31:803-805.
75. Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet 2008;371:1854-1860.
76. Man CY, Cheung ITF, Cameron PA, Rainer TH. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute gout like arthritis: a double-blind, randomized, controlled trial. Ann Emerg Med 2007;49:670-677.
77. Siegel LB, Alloway JA, Nashel DJ. Comparison of adrenocorticotropic hormone and triamcinolone acetonide in the treatment of acute gouty arthritis. J Rheumatol 1994;21:1325-1327.
78. So A, De Meulemeester M, Pikhlak A, et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: Results of a multicenter, phase II, dose-ranging study. Arthritis Rheum 2010;62:3064-3076.

79. Dalbeth N et al. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. Ann Rheum Dis 2012. doi:10.1136/annrheumdis-2011-200156.
80. Becker MA, Schumacher Jr HR, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353:2450-2461.
81. Becker MA, Schumacher Jr HR, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty eight day, multicenter, phase II, randomized, double blind, placebo controlled, dose response clinical trial examining safety and efficacy in patients with gout. Arthritis Rheum 2005;52:916-923.
82. Becker MA, Schumacher HR, et al. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. J Rheumatol 2009;36(6):1273--1282.
83. Reinders MK, Haagsma C, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day in patients with gout. Ann Rheum Dis 2009;68(6): 892-897.
84. Schumacher Jr HR, Becker MA, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28 week, phase III, randomized, double-blind, parallel group trial. Arthritis Rheum 2008;59:1540-1548.
85. Reinders MK, van Roon EN, et al. Efficacy and tolerability of urate lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. Ann Rheum Dis 2009;68:51-56.
86. Sundy JS, Baraf HSB, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA 2011;306:711-720.
87. Borstad GC, Bryant LR, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004;31:2429-2432.
88. Paulus HE, Schlosstein LH, et al. Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. Arthritis Rheum 1974;17: 609-614.
89. Karimzadeh H, Nazari J, et al. Different duration of colchicine for preventing recurrence of gouty arthritis. Journal of Research in Medical Sciences 2006;11: 104-107.
90. Ohue T, Yamamoto T, et al. Effects of allopurinol and benzbromarone on renal clearance of creatinine and uric acid in gouty patients. Jpn J Rheumatol 1991; 3:21-27.
91. Perez-Ruiz F, Calabozo M, et al. Treatment of chronic gout in patients with renal function impairment: An open, randomized, actively controlled study. J Clin Rheumatol 1999;5:49-55.
92. Hosoya T, Ichida K, et al. Combined therapy using allopurinol and benzbromarone for gout and hyperuricemia complicated with renal disorder. Jpn J Rheumatol 1992;4:77-90.
93. De Angelis S, Noce A, Di Renzo L, et al. Is rasburicase an effective alternative to allopurinol for management of hyperuricemia in renal failure patients? A double blind-randomized study. Eur Rev Med Pharmacol Sci 2007;11:179-184.
94. Stamp LK, O'Donnell JL, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum 2011;63:412-421.
95. Vazquez-Mellado J, Meono Morales E, et al. Relation between adverse events associated with allopurinol and renal function in patients with gout. Ann Rheum Dis 2001;60 (10):981-983.
96. Perez Ruiz F, Atxotegi J, et al. Using serum urate levels to determine the period free of gouty symptoms after withdrawal of longterm urate lowering therapy: a prospective study. Arthritis Rheum 2006;55:786-779.
97. Sarawate CA, Patel PA, et al. Serum urate levels and gout flares: analysis from managed care data. J Clin Rheum 2006;12:61-65.
98. Halpern R, Fuldeore MJ, et al. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. J Clin Rheum 2009;15:3-7.
99. Wu EQ, Patel PA, et al. Frequency, risk, and cost of gout related episodes among the elderly: does serum uric acid level matter? J Rheum 2009;36:1032-1040.
100. Shoji A, Yamanaka H, et al. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 2004;51:321-325.
101. Yamanaka H, Togashi R, et al. Optimal range of serum urate concentrations to minimize risk of gouty attacks during antihyperuricemic treatment. Adv Exp Med Biol 1998;431:13-18.
102. Perez Ruiz F, Calabozo M, et al. Effect of urate lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum 2002;47:356-360.
103. McCarthy GM, Barthelemy CR, et al. Influence of antihyperuricemic therapy on the clinical and radiographic progression of gout. Arthritis Rheum 1991;34:1489-1494.
104. Thiele RG, Schlesinger N. Ultrasonography shows disappearance of monosodium urate crystal deposition on hyaline cartilage after sustained normouricemia is achieved. Rheum Int 2010;30:495-503.
105. Pascual E, Sivera F. Time required for disappearance of urate crystals from synovial fluid after successful hypouricaemic treatment relates to the duration of gout. Ann Rheum Dis 2007;66:1056-1058.
106. Li Yu J, Clayburne G, et al. Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheum 2001;28:577-580.
107. Suarez-Almazor Maria E, Lopez-Olivo Maria A, et al. Febuxostat for treating chronic gout. Cochrane Database of Systematic Reviews 2010:CD008653.
108. Catton M, Schlesinger N, et al. Allopurinol for chronic gout. Cochrane Database of Systematic Reviews 2006:CD006077.
109. Alvarez H, Pal ez B, et al. Validation of the Health Assessment Questionnaire disability index in patients with gout. Arthritis Rheum 2008;59:665-669.
110. Kanbay M, Ozkara A, et al. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearence, and proteinuria in patients with normal renal functions. Int Urol Nephrol 2007;39:1227-1233.
111. Kanbay M, Ozkara A, et al. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearence, and proteinuria in patients with normal renal functions. Int Urol Nephrol 2007;39:1227-1233.
112. Siu YP, Leung KT, et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51-59.
113. El-Gamal O, El-Bendary M, et al. Role of combined use of potassium citrate and tamsulosin in the management of uric acid distal ureteral calculi. Urol Res 2012;40:219-224.
114. Singh I, Bishnoi I, et al. Prospective randomized clinical trial

comparing phytotherapy with potassium citrate in management of minimal burden (≤8 mm) nephrolithiasis. Urol Ann 2011;3:75-81.
115. Saito J, Matsuzawa Y, et al. The alkalizer citrate reduces serum uric Acid levels and improves renal function in hyperuricemic patients treated with the xanthine oxidase inhibitor allopurinol. Endocr Res 2010;35:145-154.
116. Schlesinger N, Meulemeester MD, et al. Canakinumab relieves symptoms of acute flares and improves health-related quality of life in patients with difficult-to-treat gouty arthritis by suppressing inflammation: results of a randomized dose-ranging study. Arthritis Res Ther 2011;13:1-13.
117. Chou CT, Kuo SC. The anti-inflammatory and anti-hyperuricemic effects of Chinese herbal formula Danggui-Nian-Tong-Tang on acute gouty arthritis: a comparative study with indomethacin and allopurinol. Am J Chin Med 1995;23:261-271.
118. Alloway J, Moriarty M, et al. Comparison of triamcinolone acetonide with indomethacin in the treatment of acute gouty arthritis. J Rheum 1993;20:111-113.
119. Shi X, Li GC, et al. Randomized and controlled clinical study of modified prescriptions of Simiao-Pill in the treatment of acute gouty arthritis. Chin J Integr Med 2008; DOI: 10.1007/s11655-007-9001.
120. Zou R, Zhang H, et al. Comparative study on treatment of acute gouty arthritis by electroacupuncture with different frequency. Chin J Integr Med 2006;12:212-214.
121. Ji W, Zhu X, et al. Effects of Rebixiao granules on blood uric acid in patients with repeatedly attacking acute gouty arthritis. Chin J Integr Med 2005;11:15-21.
122. Reardon JA, Stockman A, et al. Double-blind trial of feprazone and phenylbutazone in acute gout. Curr Med Res Opin 1980;6:445-448.
123. Qiu R, Shen R, et al. Treatment of 60 cases of gouty arthritis with modified Simiao tang. J Tradit Chin Med 2008;28:94-97.
124. Tsutsumi Z, Moriwaki Y, et al. Oxidized low-density lipoprotein autoantibodies in patients with primary gout: effect of urate-lowering therapy. Clin Chim Acta 2004;339:117-122.
125. Sundy J, Becker M, et al. Reduction of plasma urate levels following treatment with multiple doses of pegloticase in patients with treatment-failure gout. Arthritis Rheum 2008;58:2889--2891.
126. Fraser R, Harvard Davis R, et al. Comparative trial of azapropazone and indomethacin plus allopurinol in acute gout and hyperuricemia. J R Coll Gen Pract 1987;37:409-411.
127. Gibson T, Rodgers V, et al. Allopurinol treatment and its effect on renal function in gout: a controlled study. Ann Rheum Dis 1982;41:59-65.
128. Scott JT. Comparison of allopurinol and probenecid. Ann Rheum Dis 1966;25:623-626.
129. Schumacher R, Sundy J, et al. Rilonacept (interleukin-1 trap) in the prevention of acute gout flares during initiation of urate lowering therapy. Arthritis Rheum 2012;64:876-884.
130. Arroll B, Bennett M, et al. More allopurinol is needed to get gout patients < 0.36 mmol/L: a gout audit in the form of a before-after trial. J Primary Health Care 2009;1:315-318.
131. Takahashi S, Moriwaki Y, et al. Effects of combination treatment using anti-hyperuricaemic agents with fenofibrate and/or losartan on uric acid metabolism. Ann Rheum Dis 2003;62:572-575.
132. Rodnan G, Robin JA, et al. Allopurinol and gouty hypericaemia: efficacy of a single daily dose. JAMA 1975;231:1143--1147.
133. Miller F, Schall R, et al. The effect of benzbromarone on allopurinol/oxypurinol kinetics in patients with gout. Eur J Clin Pharmacol 1993;44:69-72.
134. Schlesinger N, Detry MA, Holland BK, et al. Local ice therapy during bouts of acute gouty arthritis. J Rheumatol 2002;29;331-334.
135. European Medicines Agency, EPAR summary for the public: Ilaris, canakinumab. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/001109/WC500031677.pdf. Accessed July 2013.

2013 ACR/ARHP ANNUAL MEETING

Boston, EUA
14 a 19 de Novembro de 2014