COMPLIANCE IN GOUT PATIENTS

Lígia Silva*, Eugenio De Miguel**, Diana Peiteado**, Alejandro Villalba**, Martin Mola**, José Pinto*, Francisco S. Ventura*

Abstract

Introduction: Despite its relative high prevalence, potential devastating clinical consequences and socio-economic impact, the existence of effective drugs to treat it, and the well recognised direct relation between acute flares and treatment interruptions and its resumption, gout is still often considered the chronic disease with the worst rate of adherence to therapy. The reason for this is unknown. We proposed to thoroughly evaluate a subgroup of patients, aiming at identifying the clinical features predictive of non-compliance, and 5 different ways to assess those.

Methods: We analysed a number of clinical, analytical and ultrasound data relating to 34 gout patients (according to the Wallace-ARA diagnostic criteria for gout 1977 and the EULAR recommendations for gout diagnosis 2006), which were followed in a specialized rheumatology consultation as part of an ongoing study for ultrasound validation in gout. To assess non-compliance, we compared the prevalence of each one of these clinical features with 5 outcomes (2 of which related to "non-compliance": self-report of non-adherence to therapy and missing consultation, and 3 other outcomes related to "non-response": gout flare(s), final serum uric acid (sUA) ≥ 6 mg/dL, and no sonographic improvement) registered during a 1 year of follow-up assessment.

Results: We have found an association between younger age, higher body mass index, previous treatment with urate lowering drugs, self-report of previous non-compliance, nephrolithiasis and hyperuricosuria and the "outcomes of non-compliance". These patients tended to be less often treated with NSAID and allopurinol, and more often treated with corticosteroid and benzbromarone during the 1 year follow-up. They have also presented higher rate of gout flares and final sUA. Evaluating the 3 "outcomes of non-response", we have noticed a tendency for association with long disease duration, self-report of previous non-compliance (frequently attributed to gout flare), higher initial sUA and kidney failure. These patients tended to be less often treated with NSAID, and more often treated with allopurinol. Gout flare correlated to self-report of non-compliance and no sonographic improvement. Sonographic non response also correlated to higher final sUA.

Conclusions: This study shows an association between some clinical features and non-compliance, but above all, and unlike the majority of other studies, it has found a correlation between non-compliance with possible causes of worst response or lower rate of treatment, such as hyperuricosuria, nephrolithiasis, kidney failure, and contraindication for NSAID treatment. The data which is based on a comprehensive and detailed clinical assessment, might point out hidden elements, which might go beyond the visible non-compliance, contributing to the frequent lack of control of the disease.

Keywords: Gout; Compliance; Adherence; Serum Uric Acid; Ultrasound.

Introduction

Gout is the most common inflammatory arthritis in men and older women; it has been estimated to affect about 1 to 1.4% of the total population, approximately 7% of men and 3% of women aged over 65 years old, but estimates vary widely, depending on population under study. Its prevalence has increased in recent decades, possibly related to population aging, increasing obesity and changing lifestyles worldwide[1-4].

It is associated with tissue deposition of monosodium urate (MSU) crystals, usually in patients with a prolonged history of hyperuricemia. It gene-

*Rheumatology Department, Hospital de São João and Faculdade de Medicina da Universidade do Porto, Portugal
**Rheumatology Department, Hospital La Paz, Madrid, Spain

rally presents as recurrent episodes of monoarthritis, causing severe pain and impairment. If left untreated, it progresses as attacks, which become increasingly frequent, reaching progressively more joints and accumulating structural damage. At the end of its clinical spectrum, it can manifest as chronic destructive polyarthritis, affecting also other tissues, such as kidney (uric acid nephropathy and nephrolithiasis), or juxta-articular and subcutaneous tissues (gouty tophi)[5]. Moreover, it has also been associated with increased cardiovascular morbidity and mortality[5,6].

Despite being known for centuries[5], its prevalence[1,4,7], its potential devastating clinical consequences, its economic impact[5,8], the existence of effective drugs[1,3,9], and the frequent and direct relation between acute flares (and higher levels of sUA) with treatment interruptions[2,7,10] and resuming, it continues to be described by several studies as the chronic disease with the worst rate of drug adherence, ranging from 26-74%[7,11-13]. The reasons for this are unknown. Probably this is due to several different conjoint factors. Many studies suggest different patient, care system or medication factors as being responsible for this, but all agree on one point: there is insufficient data[7,11,14,15].

This study aims at thoroughly evaluate a small group of patients followed in a specialized consultation, to identify clinical risk factors which can be associated with poor compliance to therapy, and it aims at presenting 5 different ways to assess this.

Methods

The patients included in this analysis are participants in a prospective study of ultrasound evaluation of gout, started in 2008, and still ongoing (preliminary results were presented at the EULAR 2010[16]). They were recruited from the outpatient rheumatology department of the Hospital La Paz, in Madrid, to a different consultation specifically created for the purposes of that study, where they had a clinical, analytical and sonographic evaluation at 1, 3, 6, 9 and 12 months from the first visit. Patients with a doubtful diagnosis of gout, and those with gout and concomitant diseases possibly associated with arthritis, such as psoriasis or cancer, were excluded from the study. A total of 34 adults aged 18 years or older, were diagnosed gout according to the Wallace-ARA diagnostic criteria for gout (1977)[17] and the EULAR recommendations for gout diagnosis (2006)[18]. All of them had hyperuricemia and at least one sonographic sign suggestive of gout at their 1st visit.

To study the risk factors of poor adherence to therapy, we have collected data from these medical registers, filling a protocol focusing on epidemiological, clinical, analytical and ultrasound aspects (Table I). We have noted several factors such as age, sex, history of excessive alcohol consumption (greater than 60 g/day), dyslipidemia, body mass index (BMI), diabetes, hypertension, time elapsed since the 1st episode of arthritis, presence of tophi, initial sUA, previous treatment with urate lowering drugs (ULD) allopurinol or benzbromarone, and prophylaxis with colchicine, NSAID or corticosteroid within the 30 days prior to its start, self-reported compliance (defined as taking medication regularly, as prescribed), and if not compliant, whether the reason was an adverse event or the worsening of the disease with gout flare(s), attributed to the drug by the patient. Besides the direct effect of some of these factors in uric acid metabolism, these were selected, in accordance to previous studies, as potentially related to poor adherence[6,7,14]. We have also collected data to assess possible causes of poor response to therapy or contraindication to NSAID or ULD, such as history of nephrolithiasis, kidney failure, medication with diuretic or low dose aspirin, and urine uric acid, since these can hinder control of the diease, causing non-compliance[4,5,19]. To assess adherence one year after the 1st evaluation, we have registered 2 "non-compliance outcomes": the medication prescribed during the 1 year follow-up and self-report of compliance to it during this time interval (or if not, whether was due to an adverse event, gout flare(s) or "other causes"), and the non attendance to one or more follow-up visits. We have also noted 3 "non-response outcomes": gout flares (defined as episodes of arthritis requiring NSAID, colchicine or corticosteroid), and if so, whether one or more joints were affected, the initial and 12th month levels of sUA, and the evolution of ultrasound signs of gout. We considered a sonographic improvement when there was a decrease in a score that resulted from the sum of the locations with hyperechoic aggregates or areas of MSU deposit and Doppler signal (semi-quantitative scale), in 20 different locations in joints and tendons in feet, ankles and knees. This is being evaluated and properly valued in the ongoing ultrasound study[16].

Table I. Main features of the population, and outcomes at the final visit

At the 1st visit:	Dropouts (n = 9 patients)	On protocol (n = 25 patients)	P
Age (mean, years ± SD)	55,7 ± 10,7	57,6 ± 12,5	0,678
Alcohol > 60 g/day (%)	55,6	56	0,982
Dyslipidemia (%)	77,8	76	0,917
(mean ± SD)	28,2 ± 2,52	27,8 ± 3,96	0,783
Diabetes (%)	22,2	32	0,594
Hypertension (%)	44,4	56	0,565
gout attack (mean, years ± SD)	9,9 ± 15,5	10,1 ± 9,02	0,964
Gout diagnosis ≤ 1year (%)	33,3	32	0,944
Previous treatment with ULD (%)	55,6	72	0,381
• Profylaxis (cochicine/ NSAID /corticosteroid) 30 days prior to ULD (%)	100	94,4	0,610
• Self-reported previous non-compliance (%)	60	83,3	0,284
• Not compliant for:			
- adverse event (%)	0	11,1	0,610
- gout flare(s) (%)	0	16,7	0,504
Tophi (%)	22,2	40	0,354
Initial sUA (mean, mg/dL ± SD)	8,3 ± 1,21	8,7 ± 1,58	0,477
Nephrolithiasis* (%)	**33,3**	**0**	**0,002***
Kidney failure (%)	11,1	8	0,786
Diuretic or low dose aspirin (%)	22,2	36	0,464
Urine uric acid:			
• > 750 mg/day* (%)	**66,7**	**21,7**	**0,035***
• < 250 mg/day (%)	16,7	21,7	0,786
Medication at 1st visit with:			
Colchicine (%)	88,9	92	0,786
NSAID (%)	**44,4**	**72**	**0,147**
Corticosteroid (%)	**22,2**	**4**	**0,104**
Allopurinol (%)	**77,8**	**96**	**0,104**
Benzbromarone (%)	0	4	0,557
At the final visit:	**Dropouts (n = 6 patients)**	**On protocol (n = 25 patients)**	**P**
Self-report of non-compliance (%)	66,7	40	0,253
Not compliant for:			
• adverse event (%)	0	8	0,373
• gout flare(s) (%)	0	8	0,373
• "forgot/ felt better" (%)	50	24	0,630
Missing ≥1 consultation* (%)	**100**	**20**	**0,001***
• ≥ 1 gout flare (%)	66,7	72	0,804
• ≥ 2 joints affected (%)	25	50	0,388
Final sUA:			
• **mean** (mg/dL ± SD)	**7,3 ± 1,19**	**6,1± 1,37**	**0,058**
• ≥ 6 mg/dL* (%)	**100**	**56**	**0,01***
• no decrease* (%)	**33,3**	**4**	**0,029***
Sonography: no improvement (%)	75	40	0,205

Legend: SD – Standard Deviation, BMI – body mass index, ULD – urate lowering drug, NSAID – nonsteroidal anti-inflammatory drug, sUA – serum uric acid.

The results were analyzed using SPSS version 10.5 software (SPSS, Chicago, IL). Comparison between means was performed using the Student's t-test for independent samples. A P value less than 0.05 was considered statistically significant.

Results

This study comprised 34 subjects with a mean age of 57,1 ± 11,8 years. Only 2 were female. Nine patients discontinued the study before completing the 1 year protocol: 3 (including 1 woman) attended only the 1st consultation, and the remaining 6 were followed for an average of 4 months. Table I presents the population's features and the 5 outcomes assessed, registered during follow-up. The 9 patients who discontinued the study were quite similar to the group of 25 who completed the protocol, except they presented more cases of hyperuricosuria and all cases of nephrolithiasis. They also tended to be less often treated with NSAID and allopurinol, and more frequently with corticosteroid.

By analyzing the records of the last visit, beyond the obvious lower adherence to medical consultation, the patients who have dropped out before the 1 year of follow-up (6 patients) had a lower rate of reduction in levels of sUA, 33,3% had no decrease at all, and none reached levels below 6 mg/dL. Similar to the previous medication for gout, also during the follow-up period, there was no mention to adverse events or exacerbation of the disease as a cause to suspend therapy, but 50% of them cited they "forgot" or "tried to suspend because felt better". In the 25 patients group on the protocol, 83,3% reported non-compliance to medication prescribed prior to this study, and of these, only 11,1% claimed to have suspended colchicine and allopurinol for adverse events (diarrhoea and worsening of arthritis, respectively). During the 1 year follow-up, 8% suspended colchicine for epigastric pain, 8% left allopurinol for gout flares, and 24% assumed forgetfulness. One patient, who had previously suspended colchicine for diarrhoea, was prescribed a lower dose, and presented good tolerance.

Focusing on the 25 patients on protocol, we have analyzed data comparing the prevalence of the clinical features observed, in relation to 5 outcomes (versus their reciprocal, as exemplified in Tables II and III): self-report of non-compliance during the 1 year follow-up, missing (≥ 1) medical consultation, having (≥ 1) gout flare(s), final sUA ≥ 6 mg/dL, and having no sonographic improvement. Table IV summarizes our most significant findings.

Comparing self-reports of "non-compliance" versus "compliance" to therapy during the follow-up, the "non-compliant" had less often urine uric acid < 250 mg/day (0% versus 35,7%, P value of 0,026). Moreover, 100% (versus 72,7%) reported they were also not compliant previously, and there was also a trend for younger age (52,6 ± 8,8 versus 61 ± 13,7 years, P = 0,101). Comparing "non-compliance" with the other 4 outcomes, self-report of non-compliance was associated to a higher rate of acute flares (90% versus 60%, P = 0,110).

Patients who "missed (≥ 1) consultation" had higher BMI (31 ± 3,4 versus 27 ± 3,8 kg/m^2, P = 0,043), and were more frequently treated with benzbromarone during follow-up (20% versus 0%, P = 0,043). None had a recent (< 1 year) diagnosis of gout (versus 40% in the reciprocal group, P = 0,09), and all of them had previously been treated with ULD.

Having "≥ 1 gout flare(s)" versus "no gout flare(s)" during the 1 year follow-up was correlated with higher self-report of non-adherence to therapy (92,9% versus 50%, P = 0,045 for treatments prescribed before, and 50% versus 14,3%, P = 0,110 for drugs prescribed during this study). Comparing this outcome with the other 4, having gout flares tended be correlated with "no sonographic improvement" (50% versus 14,3%, P = 0,110).

Besides having significantly higher sUA initial levels, patients with "final uricemia levels ≥ 6 mg/dL" (versus "< 6") (Table II) tended to report more often having suspended treatment due to gout worsening, and were less often treated with NSAID. "No sonographic improvement" tended to be associated with longer disease duration, self-report of previous non-compliance, kidney failure and gout flare(s), but the only significant correlation was the higher final sUA level (Tables II and III).

Discussion

Despite its huge impact, little is known about (non adherence) to gout treatment, its true prevalence, its causes, its consequences, and the best way to monitor and improve it. Some studies point out to different patient characteristics (such as younger age, fewer comorbid conditions, being treated with NSAID previous to ULD, male sex and some cop-

Table II. Final uricemia levels «≥ 6» versus «< 6» mg/dL at 1 year

	Final sUA ≥ 6 (n=14)	Final sUA <6 (n=11)	P
Age (mean, years ± SD)	60,1 ± 13,7	54,5 ± 10,5	0,268
Alcohol > 60 g/day (%)	57,1	54,5	0,902
Dyslipidemia (%)	78,6	72,7	0,747
BMI (mean ± SD)	28,2 ± 4,5	27,3 ± 3,2	0,621
Diabetes (%)	35,7	27,3	0,669
Hypertension (%)	50	63,6	0,516
1st gout attack (mean, years ± SD)	9,5 ± 10	10,8 ± 7,9	0,727
Gout diagnosis ≤ 1year (%)	35,7	27,3	0,669
Previous tx with ULD (%)	71,4	72,7	0,946
• Profylaxis prior to ULD(%)	100	87,5	0,276
• Self-report of previous non-compliance (%)	80	87,5	0,693
• Not compliant for:			
• **adverse event** (%)	**0**	**25**	**0,120**
• **gout flare(s)** (%)	**30**	**0**	**0,104**
Tophi (%)	35,7	45,5	0,639
Initial sUA* (mean, mg/dL ± SD)	**9,5 ± 0,9**	**7,7 ± 1,7**	**0,002***
Kidney failure (%)	14,3	0	0,207
Diuretic or low dose aspirin (%)	35,7	36,4	0,975
Urine uric acid:			
• >750 mg/dL (%)	25	18,2	0,966
• <250 mg/d (%)	33,3	9,1	0,344
Medication at 1st visit with:			
• Colchicine (%)	92,9	90,9	0,866
• **NSAID (%)**	**57,1**	**90,9**	**0,066**
• Corticosteroid (%)	7,1	0	0,387
• Allopurinol (%)	100	90,9	0,268
• Benzbromarone (%)	0	9,1	0,268
Other outcomes:			
Self-report non-compliance (%)	42,9	36,4	0,755
Missing consult (%)	14,3	27,3	0,442
Gout flare(s) (%)	71,4	72,7	0,946
Sonography: no improvement*(%)	**57,1**	**18,2**	**0,05***

ing patterns, presumably reflecting decreased motivation or level of expertise in management of the disease)[7,12,14], and health-care system or medication problems (such as low index of medical support, initiating ULD in higher doses or with no colchicine prophylaxis, and inefficacy or side effects of drugs)[1,2,12,19-22]. However, one major limitation of the few directed studies is the lack of statistical power of their findings, and the difficulty to compare among the existing studies, because they measure different things, apply to distinct populations (ethnicity, consultation contexts, causes and severity of gout), use different definitions of adherence and different methods to assess it[7,11,14,15]. Our study found a correlation of clinical features with measurements of non-compliance and non-response. Based on specialized and accurate medical records (clinical, analytical and sonographic) of two rheumatologists directed to this subject, we were able to overcome some limitations of previous studies based on administrative and pharmacists records, which presented shortcomings regarding the proper diagnosis of gout, the registration of the cause of non-adherence, the appreciation of the importance of other causes of poor adherence and the response to therapy, among

Table III. Sonographic «no-improvement» versus «improvement» at 1 year

	Sonography: no improve (n=10)	Sonography: improve (n=15)	P
Age (mean, years ± SD)	58,6 ± 11,8	57 ± 13,3	0,762
Alcohol > 60 g/day (%)	70	46,7	0,268
Dyslipidemia (%)	90	66,7	0,196
BMI (mean ± SD)	26,6 ± 4,5	28,6 ± 3,5	0,232
Diabetes (%)	20	40	0,314
Hypertension (%)	50	60	0,639
1st gout attack (mean, years ± SD)	**13,4 ± 10,2**	**7,9 ± 7,7**	**0,135**
Gout diagnosis ≤ 1year (%)	20	40	0,314
Previous treatment with ULD (%)	70	73,3	0,863
• Profylaxis prior to ULD (%)	100	90,9	0,442
• **Self-report of previous non-compliance (%)**	**100**	**72,7**	**0,146**
• Not compliant for:			
• adverse event (%)	14,3	9,1	0,926
• gout flare (%)	28,6	9,1	0,552
Tophi (%)	50	33,3	0,426
Initial sUA (mean, mg/dL ± SD)	8,9 ± 1,4	8,5 ± 1,7	0,540
Kidney failure (%)	**20**	**0**	**0,076**
Diuretic or low dose aspirin (%)	20	46,7	0,188
Urine uric acid:			
• >750 mg/dL (%)	30	15,4	0,423
• <250 mg/d (%)	20	23,1	0,867
Medication at 1st visit with:			
• Colchicine	100	86,7	0,246
• NSAID	60	80	0,295
• Corticosteroid	10	0	0,228
• Allopurinol	100	93,3	0,426
• Benzbromarone	0	6,7	0,426
Other outcomes:			
Self-report non-compliance (%)	50	66,7	0,426
Missing consult (%)	20	20	1,0
Gout flare(s) (%)	**90**	**60**	**0,110**
Final sUA* (mean, mg/dL ± SD)	**6,9 ± 1,8**	**5,6 ± 0,7**	**0,022***

others[7,23].

Similar to several previous studies, high sUA levels (≥ 6 mg/dL) tended to be associated with flares[8,10,20], and in this study, we have also found trends of correlation to "report of non-compliance" and "no signs of ultrasonic improvement", not previously evaluated. There is evidence of clinical outcomes being consistently better with sUA levels bellow 6 mg/dL, in accordance with the saturation point of MSU. This threshold has been very useful, and is the most repeatedly recommended in guidelines, for use in clinical practice and research, as a surrogate marker of efficacy and compliance to therapy[13,24,25]. However, it is an arbitrary target level that needs validation. For instance, some studies suggest that there should be a dynamic cut-off, over time. Initially, the reduction of sUA should be as slow as possible, to minimize the risk of flare, and in some subpopulations of patients, like those with tophaceous gout, sUA levels should be as low as possible. But no study has formally evaluated the effectiveness and risks of these strategies[2,26,27]. Our results come in line with this perspective. We have found trends of correlation of some clinical features like nephrolithiasis (all patients with nephrolithiasis discontinued the study), kidney fai-

Table IV. Summary of the trends of correlation found in this study

Measurements of non-compliance	Associated clinical features	Associated outcomes
Self-report of non-compliance (during the 1 year follow-up)	• Younger age • Self-report of previous non-compliance • **Less often urine uric acid < 250mg/dL***	• Gout flare(s)
Abandoning the study (before 1 year of follow-up)	• **Nephrolithiasis* +** • **Urine uric acid >750mg/dL*** • Less often treated with NSAID and allopurinol, and more often with corticosteroid during follow-up	• **Missing consultation*** • **Higher final sUA***
Missing consult(s) (during the 1 year follow-up)	• **Higher BMI*** • Gout diagnosis >1 year • Previous treatment with ULD • **Treatment with benzbromarone during follow-up***	Ø
Measurements of non-response (at 1 year)		
Gout flare(s)	• **Self-report of previous non-compliance*** • Treatment with allopurinol during follow-up	• Self-report of non-compliance (during follow-up) • No sonographic improvement
Final sUA □6 mg/dL	• **Higher initial sUA*** • Self-report of previous non-compliance because it caused gout flare (less often for adverse events) • Less often treated with NSAID during follow-up	• **No sonographic improvement***
No sonographic improvement	• Long disease duration • Self-report of previous non-compliance • Kidney failure	• Gout flare(s) • **Higher final sUA***

Legend: sUA – serum uric acid, BMI – body mass index, ULD – urate lowering drug, NSAID – nonsteroidal anti-inflammatory drug. Notes: +all patients with history of nephrolithiasis abandoned the study before 1 year of follow-up, so this factor was not taken into account in the remaining analysis of risk assessment. *statistical significance

lure and urine uric acid abnormalities, with the 5 outcomes used to measure "non-compliance" and "non-response". Our study suggests that non-response and contraindication to drugs like ULD or NSAID may be decisive as cause of non-compliance, as it hinders adjustment to medication, leading the patient to suspend it, and when trying to resume it, it aggravates the disease. So, these clinical features may mediate other pathogenic pathways that eventually redound in non-adherence by unmotivated patients[22].

The sonographic outcome was the most often related to the parameters of poor response to treatment. However, this is still a crude preliminary analysis, that needs to be confirmed, and further research (as the one that is underway on this same population) is necessary to evaluate and validate sonographic findings in gout[16,28-30]. In any case, this is consistent with the logical link that some studies demonstrate to exist between the decreased detection of urate crystals in synovial fluid (even in asymptomatic joints) or reduction in tophi area, in those patients on treatment with ULD who showed reducing levels of sUA[2,26,31,32]. The small number of participants, but more important, the lack of a control group of gout patients in outpatient treatment, reduced the statistical power of this study. These factors might explain why we didn't reach statistical significance on clinical features like dyslipidemia, hypertension or presence of tophi, but

most likely this was the result of evaluating a more homogeneous group of selected patients which presented a more severe disease, and were referred to a specialized consultation. However, in fact, this might have contributed to a concentration of markers of non-compliance (including non-response), which may have been instrumental to find new trends to guide future research.

Conclusion

Treatment and monitoring of gout must be patient-tailored, and this study suggests that there might be much more behind the apparent "psychosocial factors" determining non-adherence to therapy. We have found correlation of higher BMI, nephrolithiasis and urine uric acid abnormalities with non-compliance, which correlated to gout flare, no sonographic improvement and/ or higher sUA. Possibly, patients with different pathogenic mechanisms and contraindication or insufficient response to therapy of gout, need a different approach from the start (for instance, reinforcement of prophylaxis) and also special attention over time. Efforts should be made to standardize the best methods to assess compliance, since this is probably one main reason for gout widespread suboptimal care. Frequent regular consultations (as 1 month interval, at onset), with quantification of improvement by clinical, analytical and, sometimes, ecographic means, can be a very rewarding strategy.

Correspondence to
Lígia Silva
Serviço de Reumatologia do Hospital de São João,
Alameda Professor Hernâni Monteiro
4202-451 Porto, Portugal
E-mail: ligia1silva@yahoo.com

References

1. Mikuls TR. Quality of care in gout: from measurement to improvement. Clin Exp Rheumatol 2007;25:114-119.
2. Perez-Ruiz F, Lioté F. Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? Arthritis Rheum 2007;57:1324-1328.
3. Baker JF, Ralph Schumacher H. Update on gout and hyperuricemia. Int J Clin Pract (published online) 2009 Nov. doi:10.1111/j.1742-1241.2009.02188.x
4. Doherty M. New insights into the epidemiology of gout. Rheumatology (Oxford) 2009;48:2-8.
5. Gibson T. Cristal-related arthropathies. In: Hochberg M, Silman A et al, ed. Rheumatology. 4th ed. Mosby Elsevier; 2008. 2:p1805-1837.
6. Ioachimescu AG, Brennan DM, Hoar BM, Hazen SL, Hoogwerf BJ. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. Arthritis Rheum 2008;58:623-630.
7. Harrold LR, Andrade SE, Briesacher BA et al. Adherence with urate-lowering therapies for the treatment of gout. Arthritis Res Ther 2009;11:R46.
8. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls TR. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. Curr Med Res Opin 2009;25:1711-1719.
9. Terkeltaub R, Zelman D, Scavulli J, Perez-Ruiz F, Lioté F. Gout Study Group: Update on hyperuricemia and gout. Joint Bone Spine 2009;76:444-446.
10. Shoji A, Yamanaka H, Kamatani N. 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.
11. Harrold LR, Andrade SE. Medication adherence of patients with selected rheumatic conditions: a systematic review of the literature. Semin Arthritis Rheum 2009;38:396-402.
12. de Klerk E, van der Heijde D, Landewé R, van der Tempel H, Urquhart J, van der Linden S. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. J Rheumatol 2003;30:44-54.
13. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy 2008;28:437-443.
14. Harrold LR, Andrade SE, Briesacher B et al. The dynamics of chronic gout treatment: medication gaps and return to therapy. Am J Med 2010;123:54-59.
15. Riedel AA, Nelson M, Joseph-Ridge N, Wallace K, MacDonald P, Becker M. Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. J Rheumatol 2004;31:1575-1581.
16. D. Peiteado Lopez, A. Villalba, E. De Miguel, M.C. Ordoñez, E. Martín Mola. Longitudinal study of ultrasonography sensibility to change in patients with gout after one year of treatment. Ann Rheum Dis 2010;69:713.
17. Wallace S L, Robinson H, Masi A T, Decker J L, McCarty D J, Yu T F. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895-900.
18. Zhang W, Doherty M, Pascual E et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1301-1311.
19. Pillinger MH, Keenan RT. Update on the management of hyperuricemia and gout. Bull NYU Hosp Jt Dis 2008;66:231-239.
20. Sarawate CA, Patel PA, Schumacher HR, Yang W, Bre-

wer KK, Bakst AW. Serum urate levels and gout flares: analysis from managed care data. J Clin Rheumatol 2006;12:61-65.
21. Singh JA. Quality of life and quality of care for patients with gout.Curr Rheumatol Rep 2009;11:154-160.
22. Singh JA, Hodges JS, Asch SM. Opportunities for improving medication use and monitoring in gout. Ann Rheum Dis 2009;68:1265-1270.
23. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf. 2006;15:565-74; discussion 575-7.
24. Zhang W, Doherty M, Bardin T et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312--1324.
25. Perez-Ruiz F. Treating to target: a strategy to cure gout. Rheumatology (Oxford) 2009;48:ii9-ii14.
26. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum 2002;47:356-360.
27. Hershfield MS. Reassessing serum urate targets in the management of refractory gout: can you go too low? Curr Opin Rheumatol 2009;21:138-142.
28. Thiele RG, Schlesinger N. Diagnosis of gout by ultrasound. Rheumatology 2007; 46:1116-1121.
29. Carter JD, Kedar RP, Anderson SR et al. An analysis of MRI and ultrasound imaging in patients with gout who have normal plain radiographs. Rheumatology (Oxford) 2009;48:1442-1446.
30. Perez-Ruiz F, Dalbeth N, Urresola A, De Miguel E, Schlesinger N. Imaging of Gout: findings and utility. Arthritis Research & Therapy 2009;11:232-239.
31. Li-Yu J, Clayburne G, Sieck M et al. Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol 2001;28:577-5780.
32. Becker MA, Schumacher HR Jr, Wortmann RL et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353:2450--2461.

SPI International School of Immunology 2011

Tavira, Portugal
28 Março a 01 Abril 2011

31st Workshop for Rheumatology Research (EWRR)

Amesterdão, Holanda
3 a 06 Março 2011