Allopurinol in Inflammatory Arthritis (probably Gout): Indian Perspective in Light of EULAR Recommendations

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Research Article

Abstract: **Introduction-**Hyperuricemia (solubility point of Mono Sodium Urate Crystal i.e. 7.1 mg/dl) is associated with gout and present in 0.2 to 2% of Indian popultion. EULAR has published the guidelines for the diagnosis of gout based on evidences. In this study, we tried to evaluate clinical correlation of arthralgia with serum uric acid level in Indian patients and benefit from Allopurinol treatment. **Material and Methods-Study design** - Prospective, open labeled single arm Study carried out in Hospital attached to Medical University. **Exclusion Criteria were** Patients having definitive diagnosis for the etiology of arthralgia or Definitive Gout by clinical diagnosis as per EULAR recommendation. **Inclusion criteria were** Patients having the history of use of analgesic with persistent symptoms, having less than 4 EULAR criteria for gout and willing to be enrolled in the study. **Intervention -** Allopurinol 100 mg twice a day was given to patients and clinically assessed on day 1, day 10 and at 4 week **Sample size: 28** patients were included in the study and follow up. Results – In elderly age group incidence is same in both sexes. Purine rich diet increases the risk five times with more risk of precipitation of symptoms at lower level of uric acid. Most common site of presentation was knee pain i.e. 50%. Serum Uric acid at enrollment was 6.76±0.99 that reduced to 3.74±0.63 at four week with dissolving of symptoms. **Conclusion**–There is a subset of Gout in elderly Indians, which is more prone to precipitation of symptoms at lower level of serum Uric acid and equal gender distribution. Hyperuricemia in patients may be defined on 5.0 mg% and target level should be kept less than 4.0 mg in Indians.

Key words: Gout, Indian, EULAR, Allopurinol.

Introduction

Theoretically hyperuricemia is defined as solubility point of Mono Sodium Urate Crystal i.e. 7.1 mg/dl however practically it is defined as more than 2 SD of mean level in population. Although hyperuricemia is not an indication of therapy[1] it is associated with gout and nephrolithisis[2] and present in 0.2 to 2% of Indian popultion[3]. Level of uric acid more than 6.5 mg/dL is associated with obesity, diabetes, and increased cardiovascular risk[4-6].

19% of the people who have increased serum uric acid are suffering from gout[7]. Risk factors associated with gout are purine rich food, alcohol, and over weight[8-10]. Incidence of gout is correlated positively with serum uric concentration especially with uric acid more than 8.0 mg/dL[11]. In general practice gouty arthritis is more common than rheumatoid arthritis[12]. Man has up to 9 times more risk than woman due to protective effect of estrogen in women[5].

EULAR has published the guidelines for the diagnosis of gout based on evidences[13-14].

For diagnosis of gout the best time to do serum uric acid level is 2 weeks after the attacks when acute symptoms subside[15-17]. In this study, we tried to evaluate clinical correlation of arthralgia with serum uric acid level in Indian patients and benefit from Allopurinol treatment.

Material and Methods-

Study design - This Prospective, open labeled single arm Study was carried out during 1st July 2007 to 30 May 2012 in Department of Orthopedic in Hospital attached to medical University, Kolhapur.

Exclusion Criteria were

1. Patients having definitive diagnosis for the etiology of arthralgia
2. Definitive Gout by clinical diagnosis as per EULAR recommendation i.e. 4 out 7 criteria were present

Inclusion criteria were

1. Patients having the history of use of analgesic with persistent symptoms
2. Having less than 4 EULAR criteria for gout
3. Willing to be enrolled in the study.

Intervention - Allopurinol 100 mg twice a day was given to patients and clinically assessed on day 1, day 10 and

at 4 week to record the pain score with the help of 5-point Linkert scale by patient. Joint swelling, tenderness and Erythema were assessed by physicians on the same scale. Serum uric acid level was repeated at 4 week.

Sample size: 28 patients were included in the study and followed up.

Results- Their demographic data were as follows:

Gender ratio –Male were slightly more than female but difference were non-significant. (Refer Figure 1) ($p > 0.05$)

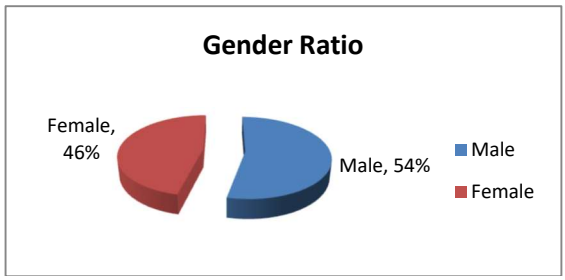

Figure 1 *Gender Ratio*

Age (years)

Age of all patients were 45.89±14.00 years while Male were 46.6±16.32 years and Female were of 45.08±11.38 years. (Refer Figure 2)

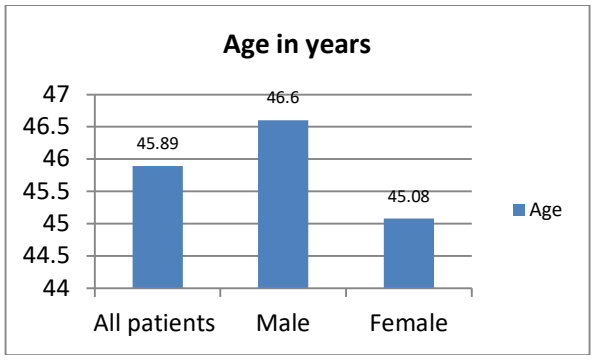

Figure 2 *age in years*

Dietary habits

Nonvegetarian i.e. purine rich diet were present in 82% of patients with frequency of 2 to 5 times per week. (Refer Figure 3)

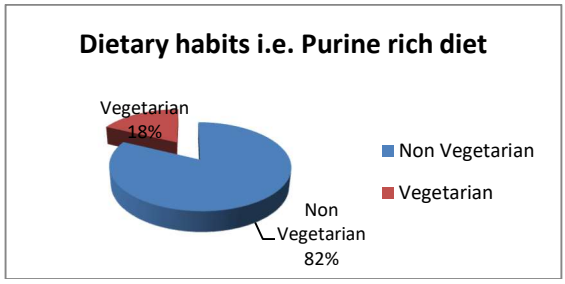

Figure 3 *Non Vegetarian Vs Vegetarian*

Presenting symptoms:

Lower extremities involvement was the commonest presentation, accounted for 68% of patients. 50% of patients were having knee pain either unilateral or bilateral. Upper extremities was involved in 7% while 18% patients were presented with multiple joint pain i.e. more than 5 joints were involved. (Refer Figure 4)

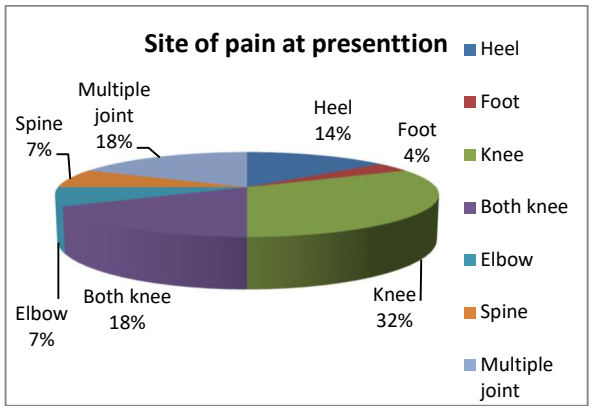

Figure 4 *Presenting symptoms*

Serum uric acid:

Serum uric acid was 6.76±0.99 at enrollment in all patients but male have higher level of SUA (7.23±0.78) as compare to female (6.22±0.95). Difference in mean SUA was also seen in Non-vegetarian (6.62±0.96) as well as vegetarians (7.4±0.97). SUA was classified into different subclass i.e. 5-, 6-, 7- 8-mg%. There representation was as follows: (Refer Figure 5)

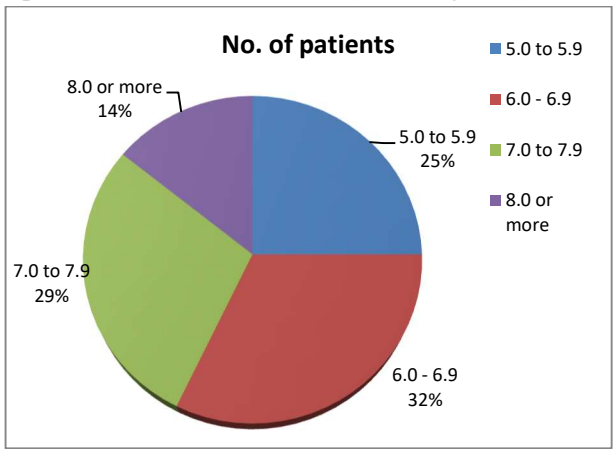

Figure 5 *Serum Uric acid level in patients*

It is seen that 75% patients were having hyperuricemia (uric acid 6.0 mg% or more) as per newer cut off point.

Presence of EULAR criteria's for clinical diagnosis–

EULAR has recommended the criteria's for clinical diagnosis of Gout as per the diagnostic ladder. They are as follows in increasing order –

1. Rapid pain and swelling
2. Erythema
3. Podegra

4. Hyperuricemia more than 6 mg%
5. Definitive tophi
6. X- ray
7. MSU crystals in joint fluid aspirate

For clinical diagnosis probability is 82.29% if first 3 criteria are fulfilled which increases to 99% if hyperuricemia is also present.

In this study, Pain, swelling and erythema was present in all the patients while podegra was present in none. On the basis of above presenting symptoms and taking cut off point of 6.0 mg%, only 75% patients were fulfilling 3 out of 7 criteria while remaining 25% were having 2 criteria's with uric acid between 5.0 to 6.0 mg%. An MSU crystal in joint aspiration fluid was not done due to non feasibility in given set up. (Refer Figure 6)

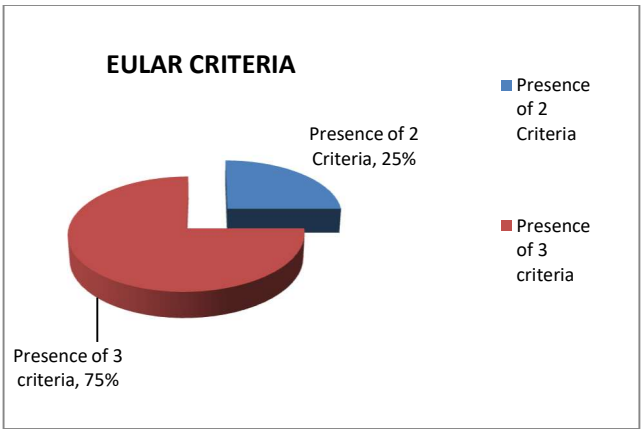

Figure 6 *Number of Eular criteria present in patients*

Improvement in pain – It was the patient accessed criteria. Pain score was recorded on 5 point scale by the patient on day 1, day 10 and at 4 weeks. Pain score was 57 on day 1 that reduced to 10 on day 10 and 0 on 4 week. (Refer Table 1)

Table 1: Improvement in Pain score

Parameter		**On enrollment (Day 1)**	**1st follow up (Day 10)**	**2nd follow up (4 week)**
Pain as per Linkert Scale (score)	None (0)	0 (0.00%)	19 (67.86%)	28 (100%)
	Mild (1)	1(3.57%)	8 (28.57%)	0 (0.00%)
	Moderate (2)	25(89.29%)	1 (3.57%)	0 (0.00%)
	Severe (3)	2 (7.14%)	0 (0%)	0 (0.00%)
	Extreme(4)	0 (0.00%)	0 (0%)	0 (0.00%)
	Total score	57	10	0
Value of paired in student t test **a**t t_{27} on the respective follow up as compared to previous visit			18.68, P<0.001	3.38, P<0.01

Improvement in tenderness: Tenderness score was 49 at presentation that reduced to 20 at first follow up and 1 at four week. (Refer Table 2)

Table 2: Improvement in tenderness

Parameter		**On enrollment (Day 1)**	**1st follow up (Day 10)**	**2nd follow up (4 week)**
Tenderness as per Linkert Scale (score)	None 'no pain' (0)	0 (0.00%)	16 (57. 14%)	27 (96.43%)
	Mild 'pain'(1)	9 (32.14%)	4 (14.29%)	1 (3.57%)
	Moderate 'pain and winces' (2)	17 (60.71%)	8(28.57%)	0 (0.00%)
	Severe 'pain; winces and withdraws' (3)	2 (7.14%)	0 (0.0%)	0 (0.00%)
	Total score	49	20	1
Value of paired t test **a**t t_{27} on the respective follow up as compared to previous visit			7.91, P<0.001	4. 16, P<0.001

Improvement in swelling:

Swelling was accessed by the doctor on 4 point scale as follows and scores were given. On day one score was 37 that reduced to 7 on first follow up and to 0 at 4 week. (Refer Table 3)

Table 3: Improvement in swelling

Parameter		On enrollment (Day 1)	1st follow up (Day 10)	2nd follow up (4 week)
Swelling as per Linkert Scale (score)	None 'no swelling' (0)	0 (0.00%)	22 (78.57%)	28 (100%)
	Mild 'palpable'(1)	20 (71.43%)	5 (17.86%)	0 (0.00%)
	Moderate 'visible' (2)	7 (25.00%)	1 (3.57%)	0 (0.00%)
	Severe 'bulging beyond the joint margins' (3)	1 (3.57%)	0 (0.00%)	0 (0.00%)
	Total score	37	7	0
Value of paired t test **a**t t_{27} on the respective follow up as compared to previous visit			21.62, P<0.001	2.55, P<0.02

Improvement in erythema – Presence of erythema was scored 28 on presentation which reduced to 23 on first follow up and to 4 on four week. (Refer Table 4)

Table 4: Improvement in erythema

Parameter		On enrollment (Day 1)	1st follow up (Day 10)	2nd follow up (4 week)
Erythema	Absent (0)	00 (00%)	05 (17.86%)	24(85.71%)
	Present (1)	28 (100%)	23 (82.14%)	4 (**1**4.29%)
	Total score	28	23	4
Value of paired t test **a**t t_{27} on the respective follow up as compared to previous visit			2.42, P<0.05	7.55, P<0.001

Improvement in serum uric acid: serum uric acid has reduced significantly in all patients and was between 3.5 to 4.0 mg% on average at the end of four week. (Refer Table 5)

Table 5: Improvement in serum uric acid

Serum uric acid	On enrollment (Day 1)	2nd follow up (4 week)	T test	P value
All patient	6.76±0.99	3.74±0.63	t_{27} =13.62	<0.001
Male	7.23±0.79	3.98±0.66	t_{14} = 12.22	<0.001
Female	6.22±0.95	3.46±0.46	t_{12} = 9.43	<0.001
Nonvegetarian	6.62 ±0.96	3.76±0.63	t_{22} = 11.94	<0.001
Vegetarian	7.4±0.97	3.67±0.72	t_4 = 6.90	<0.01

Discussion

In this study male and female were in equal ratio in contrast to male predominance in Gout. It may be due to loss of protective effect of estrogen in female[18] because the patient age group was similar in both male and female and female were of postmenopausal group. In this age group, there is age related increase in other metabolic disease like diabetes, hyperlipidemia and hypertension[19-21], malignant hypertension[22-23], nephropathy[19-21] which independently increase the retention of uric acid[24-29].

5 times more incidence in non vegetarian points to importance of purine rich diet as important associated factor in joint pain and reduction in purine intake may be one of the important measure in reduction of joint pain. In addition symptoms are seen at lower level of uric acid in non vegetarian as compare to vegetarian. It again may be correlate the increase sensitivity to precipitation of symptoms in non vegetarians.

In contrast to pain in small joint, in this study half of the patients were having the pain in knee joint, while small joint were involved in only 18% of the patient.

Only 75% patients were having the hyperuricemia i.e. SUA more than 6.0 mg% while remaining have the uric acid between 5.0 to 6.0 mg%. Concentration of serum uric acid becomes more important in light of EULAR recommendation for diagnosis of gout. In our study group, Patients were not fulfilling the EULAR criteria for gout. 75% patients were satisfying 3 criteria while 25% were satisfying only 2 i.e. pain, swelling and erythema.

In our case, if cut off point be made at 5.0 mg% than all patient may satisfy at least 3 criteria of EULAR recommendation and goal of treatment may be kept at around 4.0 mg%. Shrivastava and Gaur also has recommended the treatment of hyperuricemia if more than 5.0 mg% and found most of the symptomatic patients had SUA between 5.0 to 7.0 mg%.[33]

In one study association between MSU crystals in synovial fluid and serum uric acid was established concluding median SU acid level less than 5.85 for absence of MSU in synovial fluid[37]. Many authors recommend keeping the uric acid level below 6.0 mg% in symptomatic patients.[13-14, 30-32] Patients with SU less

than 6 have 6 times less risk of acute attack and have better prognosis[32].

Patients were treated empirically with Allopurinol and benefited which may point out the separate entity of gout in Indian perspective. Indians are different genetically in predisposition and prognosis of many diseases including diabetes. That leads to different diagnostic criteria's in Indian population.

As SUA is positively correlated with cardiovascular risk factors, it needs to be addressed with special care. Urate Lowering Therapy is associated with improved clinical out come[34] and reduced frequency of attacks[35] and improvement in renal function[36].

Although EULAR has recommended the threshold to less than 6 mg%[14], it is an arbitrary level. There are studies with evidences that lower the SU better the outcome[32, 37]. Tophi are also dissolved with greater velocity and completely when SU was less than 4 mg%.[37-38] There was suggestion to reduce SU less than 5 mg% to deplete urate stores and to prevent further attack[39]. There is a question to determine which one to be followed static cutoff level (predefined level of Uric acid in mg %) or continuous cut off level (lower the better) as is the case with lipid levels in blood.[40]

Conclusion

Indian patients are more prone to inflammatory arthritis probably gout if 3 out of 7 criteria of EULAR recommendation is used for diagnosis with cut off level of serum uric acid 5.0 mg% in inter critical period. These criteria are more important in elderly patients (including post menopausal women), where the incidence of gout is similar in both male and female.

References

1. Ruilope LM, Garcia PJ. Hyperuricemia and renal function. Curr Hypertension Rep. Madrid. 2001; 25-30.
2. Campion EW, Glynn RJ, De Labry LO. Asymtomatic hyperuricemia. Risk and concequences in normative aging study. Am J Med.1987; 82: 421-426.
3. Smith C, Menon GN. Practical Rheumatology, ed 2000: pg. 337-356.
4. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR Jr, Saag KG: Gout epidemiology: results from the UK General Practice Research Database, 1990–1999. Ann Rheum Dis 2005; 64: 267–72.
5. Annemans L, Spaepen E, Gaskin M, et al.: Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. Ann Rheum Dis 2008; 67: 960–6.
6. Feig DI, Kang DH, Johnson RJ: Uric acid and cardiovascular risk. N Engl J Med 2008; 359: 1811–21.
7. Brand FN, McGee DL, Kannel WB, Stokes J 3rd, Castelli WP: Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. Am J Epidemiol 1985; 121: 11–8.
8. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G: Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004; 350: 1093–103.
9. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G: Alcohol intake and risk of incident gout in men: a prospective study. Lancet 2004; 363: 1277–81.
10. Julius U, Schulze J, Hanefeld M: Ätiologie und Pathogenese des Metabolischen Syndroms. Diabetes und Stoffwechsel 2005; 14: 333–49.
11. Schröder HE: Gicht. In: Hartmann F, Philipp T (eds.): Klinik der Gegenwart. München, Wien, Baltimore: Urban und Schwarzenberg 1993; 1–48.
12. Alamanos Y, Voulgari PV, Drosos AA : Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum 2006; 36: 182–8.
13. 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: 1301–11.
14. 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: 1312–24.
15. Urano W, Yamanaka H, Tsutani H et al.: The inflammatory process in the mechanism of decreased serum uric acid concentrations during acute gouty arthritis. J Rheumatol. 2002; 29: 1950-3.
16. Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA: Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004; 31: 2429–32.
17. Jordan KM, Cameron JS, Snaith M et al.: British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG): British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology (Oxford) 2007; 46: 1372–4.
18. Nichols A , Suiath ML, Scott JT. Effect of the oestrogen therapy on plasma and urine level of the uric acid. Br Med J. 1973; 1: 449-451.
19. Cannon PJ, Simson WB, Demartini FE et al. Hyperuricemia in primary and renal hypertension. N Engl J Med. 1966; 275; 457-65.
20. Levya F, Anker S, Swam JW et al. Serun uric acid as an index of impaired oxydative metabolism in chronic heart failure. Eur Heart J.1997; 18:858-65.
21. Messerli FH, Frohlich ED, et al. Serum uric acid in essential hypertension: an indication of the renal vascular involvement. Ann Intern Med. 1980; 93:817-827.
22. Lossa F, Farinaro E, Panica S et al. Serum uric acid and hypertension: the Olivetti heart study. J Hum Hypertens. 1994; 8:677-681.
23. Selbly IV, FriedhmanGD, Quesenberry CP et al.

Precursors of essential hypertension: pulmonary function heart rate uric acid, serum cholesterol, and other serum chemistries. Am J Epidemiol. 1990; 131:1017-1027.
24. Rathmann W, Funfhouser E, Dyer AR, Roseman JM. Relation of the hyperuricemia with various components of insulin resistant syndrome in young black and white adults. Ann Epidemiol. 1998; 8: 250-261.
25. Ficchini F, Chen YDI, Hollenback CB, et al. Relation between the resistant to insulin mediated glucose uptake, urinary uric acid clearance and plasma uric acid concentration. J Am Med Assoc. 1991; 266: 30083009.
26. Cappucio FD, Strazullo P, Farinaro E. Uric acid metabolism and tubular sodium handling: results from population based study. J Am Med Assoc. 1993; 270: 354-59
27. Lee J, Sparrow D, Vokanos PS et al. Uric acid and coronary heart disease risk: evidence for a role of uric acid in obesity insulin resistant sysdrome. Am J Epidem. 1995; 142:288-294.
28. Kerntz AL. Insulin resistace. Br Med J. 1996; 313: 1385-89. Mohan M, Halkin H, Karasik A, Lusky A. Elevated serum uric acid a facet of huperinsulinimia. Diabetologia. 1987; 30: 713-718
29. Solomma VV, Tuomilehto J, et al. Hypertriglycerimia in different degree of glucose intolerance in finish population: based study.Diabetes Care. 1992; 15:657-65.
30. Loebl WY, Scott JT: Withdrawal of allopurinol in patients with gout. Ann Rheum Dis 1974; 33: 304–7.
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: 577–80.
32. 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: 321–5.
33. Srivastava DC, Gaur SC. Evaluation and assessment of the symptomatic uricaemia in vegetarian population. Indian J Orthop 2005;39:117-20
34. Perez-Ruiz F, Calabozo M, Fernandez-Lopez MJ, Herrero-Beites A, Ruiz-Lucea E, Garcia-Erauskin G, 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.
35. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005; 353:2450–61.
36. Perez-Ruiz F, Calabozo M, Herrero-Beites AM, Garcia-Erauskin G, Pijoan JI. Improvement of renal function in patients with chronic gout after proper control of hyperuricemia and gouty bouts. Nephron 2000; 86:287–91.
37. 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; 47:356–60.
38. McCarthy GM, Barthelemy CR, Veum JA, Wortmann RL. Influence of antihyperuricemic therapy on the clinical and radiographic progression of gout. Arthritis Rheum 1991; 34: 1489–94.
39. Schumacher HR. Crystal-induced arthritis: an overview. Am J Med 1996; 100:46S–52S.
40. FERNANDO PEREZ-RUIZ1 AND FRE´DE´RIC LIOTE.´ Optimal Target for Improving Clinical Outcomes in Gout? Arthritis & Rheumatism (Arthritis Care & Research) 57; 7:2007:1324–1328.

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