

Characteristics and management of gout patients in Europe: data from a large cohort of patients

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Abstract. – OBJECTIVE: To increase the knowledge of epidemiology and treatment of gout in a 'real-life' setting, we conducted a large observational analysis (CACTUS) in two European countries, namely France and Greece.

PATIENTS AND METHODS: This was a multi-center, cross-sectional, observational analysis, conducted in France and Greece. The analysis was conducted in a field-practice scenario, with both general practitioners and rheumatologists recruiting patients for inclusion. Treatment methods and drug prescriptions were left to the sole initiative of the participating physicians. A number of epidemiological and clinical characteristics were recorded in a single inclusion visit. Compliance to maintenance treatment was also monitored after the inclusion visit by monthly interview.

RESULTS: In total 3079 patients were included. Hypertension was the most common co-morbidity (68%), followed by hypercholesterolemia (59%) and obesity (48%). Mean serum Uric Acid (sUA) concentration was 8.7 mg/dl. Almost all patients received life-style or dietary recommendations. At inclusion, 81.5% of patients were on a urate-lowering treatment. Most of these patients had been treated with allopurinol; this treatment had been interrupted for lack of reduction of sUA levels below 6 mg/dl (47%), lack of symptom relief (34%) or poor compliance (23%). At the inclusion visit, 98% of the patients were prescribed an urate-lowering treatment: 87% received febuxostat and 12% allopurinol alone. Satisfactory or very satisfactory compliance to febuxostat was recorded in 92% of the patients, versus 82% in patients on allopurinol.

CONCLUSIONS: CACTUS provides an overview of characteristics of gouty patients and gout management. Education of patients by healthcare providers seem to be a pre-requisite to optimize the management of gout, a condition which remains poorly managed.

Key Words:

Comorbidities, Epidemiology, Gout, Urate-lowering therapies.

Introduction

Gout is caused by monosodium urate crystal deposits^{1,2}. It has been estimated that 1-2% of adults in Western Countries are affected from gout^{1,4}; of note, both the prevalence and the incidence of gout have raised in the last decades⁵⁻¹¹. This recent increase can be attributed, at least partly, to the increased age of population in industrialized countries, a factor which is directly correlated with hyperuricaemia and gout¹². In addition, a number of other risk factors contribute to an increased risk of these conditions including renal impairment, high purine rich diet¹³, alcohol consumption^{14,15} and consumption of fructose-rich sodas¹⁶. Other conditions like overweight and obesity are also associated with hyperuricemia^{17,18}. Patients with hyperuricaemia with or without deposition carry a higher risk of hypertension than normotensive subjects and also increased concentrations of serum uric acid (sUA) lead to higher risk of cardiovascular events and mortality^{1,18}. Noteworthy, hypertensive agents such as diuretics, blockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers are associated with an increased risk of hyperuricaemia and incident gout¹⁹. Moreover, metabolic syndrome is strongly correlated with the disease^{20,21}.

The cornerstone of effective gout management is the persistent reduction of sUA levels below 360 mol/L (6.0 mg/dl)²². This goal can be pursued by the long-term administration of xanthine oxidase inhibitors. Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine and then xanthine to uric acid. The inhibition of this enzyme can be achieved by XO inhibitors such as allopurinol or febuxostat.

“Real-life” epidemiological information on the characteristics of gouty patients and the treatment of gout is still scant, while gout remains a disease which is curable but often poorly managed^{11,23-25}. Of note, well-conducted epidemiological and observational studies can complement evidence from clinical trials, and provide information on comorbidities and treatment. In order to increase the knowledge of epidemiology and treatment of gout in a ‘real-life’ setting, we conducted a large observational analysis in two European countries, namely France and Greece.

Patients and Methods

Setting and Design

This was a multicenter, observational analysis, conducted in France and Greece from November 2010 to October 2011. The analysis was conducted in a field-practice scenario, with both general practitioners and rheumatologists recruiting patients for inclusion. GPs and rheumatologists were asked to participate if they were known to treat gout patients, according to a dedicated registry available to the researchers. All evaluated patients signed an informed consent to the use of their data for research purposes.

Patients

Adult patients (age ≥ 18 years) could be enrolled if they were diagnosed with gout, according to physician’s medical evaluation. Patients enrolled in a clinical trial evaluating a gout treatment and pregnant or breast-feeding women were not considered. To avoid bias, each physician was asked to enroll a maximum of 3 patients.

Treatment

Treatment methods and drug prescriptions were left to the sole initiative of the participating physicians.

Data Collection

Data were recorded for each patient through a Case Report Form (CRF) in a single inclusion visit. In the CRF, the following information were recorded: age, gender, highest known sUA value, sUA value at diagnosis, current maintenance treatment prescribed/ongoing and dosage (expressed as daily dosage), any prophylactic treatment of acute attacks, and compliance (assessed

by patients’ self-reporting or evaluation of medication possession ratio). Compliance to maintenance treatment was also monitored after the inclusion visit by monthly phone interview.

Data Analysis

Data were analyzed by descriptive statistics. All data were analyzed separately for France and Greece cohorts, and then pooled by applying a weight according to the estimated variability between the two cohorts.

All data reported that were directly comparable have been used for a statistical test of homogeneity between the French and Greek populations; this statistical comparisons between the French and Greek proportions of patients was expressed as odds ratio (OR). All ORs were calculated with the French odd at the numerator, which means that an OR value greater than one represents a greater percentage of French patients compared to the Greek one. A p -value < 0.05 was considered statistically significant.

Results

Patients

In total 3079 patients were included (82.6% men; mean age 63 years). In Greece, 635 patients were enrolled by 213 investigators. In France, a total of 2444 patients were enrolled by 1133 participating physicians. The demographical data of the French cohort have been discussed in detail elsewhere²⁶.

Participating physicians were distributed uniformly throughout all areas of France and Greece.

Baseline Characteristics

Table I depicts baseline and clinical characteristics of patients. Hypertension was the most common co-morbidity (68%), followed by hypercholesterolemia (59%) and obesity (48%). With respect to risk factors, 28% of patients were smokers, 44% had an alcohol consumption >2 glasses/day, and 14% was used to drink more than one glass/day of non-diet sodas. Overall, patients with gout from Greece have more often hypertension, diabetes, and dyslipidaemia as compared to the French patients (Table II). Concomitant treatments are summarized in Table II: 26.1% of patients were on low-dose aspirin, a potential risk factor for the onset of hyperuricemia and gout.

Table I. Baseline and clinical characteristics of the study cohort.

	Unit	N	French Cohort	Greek Cohort	Pooled percentage/weighted mean	OR/difference (French vs Greek cohort)	95% C.I.	p-value
Demographic variables								
Proportion of males	%	3079	83.2	80.2	82.6	1.2	0.9 – 1.5	0.0701
Mean age (years)	Years	3079	63.9 (12)	62 (11.5)	63.5 ± 11.9	1.9	0.8 – 2.9	0.0003*
Family history of gout	%	1988	37.2	28.9	35.3	1.4	1.1 – 1.8	0.0012*
Height	cm	3059	171.4 ± 7.9	172.1 ± 7.4	171.6 ± 7.8	-0.7	-1.3 – -0.1	0.0368*
Weight	Kg	3066	85.8 ± 15.6	87.4 ± 15.3	86.2 ± 15.5	-1.5	-2.9 – -0.2	0.023*
Body Mass Index	Kg/m ²	3057	29.2 ± 4.8	29.5 ± 4.6	29.3 ± 4.7	-0.2	-0.7 – 0.1	0.1611
Waist circumference	Cm	2717	103.3 ± 12.9	105.3 ± 14.9	103.6 ± 13.4	-2.0	-3.3 – -0.6	0.0032*
Medical history and comorbidities								
HT ≥ 130/85 mmHg or ongoing treatment	%	3065	66.3	74.7	68.1	0.6	0.5-0.8	< 0.0001*
Obesity	%	3072	46.9	50.2	47.6	0.8	0.7 – 1.0	0.1389
Type 2 diabetes	%	3066	22.6	30.4	24.2	0.6	0.5 – 0.8	< 0.0001*
Smoking	%	3057	24.1	42.8	28.0	0.4	0.3 – 0.5	< 0.0001*
Hypercholesterolemia	%	3052	49.9	59.2	51.8	0.6	0.5 – 0.8	< 0.0001*
Hypertriglyceridaemia	%	3027	39.2	41.9	39.8	0.9	0.7 – 1.0	0.2321
Congestive heart failure	%	3055	7.0	3.8	6.4	1.9	1.2 – 2.9	0.0031*
Ischemic heart disease/ myocardial infarction	%	3057	10.5	8.7	10.1	1.2	0.9 – 1.6	0.1882
Chronic renal failure (GFR < 60 ml/min)	%	3035	9.5	5.2	8.6	1.9	1.3 – 2.7	0.0006*
Cancer	%	3048	2.5	3.4	2.7	0.7	0.4 – 1.1	0.197
Hepatic Failure	%	3043	1.9	1.1	1.8	1.7	0.8 – 3.9	0.1536
Liver function test abnormalities	%	2999	10.2	9.4	10.0	1.1	0.8 – 1.4	0.5184
Uric lithiasis	%	2962	6.7	14.5	8.3	0.4	0.3 – 0.5	< 0.0001*
Alcohol and drink consumption								
Alcohol consumption (> 2 glasses/day or > 30 gr alcohol/day)	%	3033	47.2	33.2	44.3	1.8	1.4 – 2.1	< 0.0001*
Beer consumption with or without alcohol ≥ 1 glasses/day)	%	3027	27.1	33.9	28.5	0.7	0.6 – 0.8	0.0007*
Non-diet soft drink consumption (≥ 1 glasses/day)	%	2999	11.0	27.7	14.5	0.3	0.2 – 0.4	< 0.0001*

Initial Diagnosis of Gout and SUA Level

Table III documents information on the initial diagnosis of gout and SUA levels. Initial diagnosis of gout was performed 5.2 years before the inclusion visit. At inclusion, mean sUA concentration was 8.7 mg/dl; about 11% of patients had tophi with a mean of 3.1 tophi/patient.

Diagnosis of gout was performed, in 74% of cases, by the treating physician. This diagnosis was confirmed, in most cases, by the presence of hyperuricemia (97%), in association with the clinical presentation. Only a small percentage of patients (6%) were diagnosed by the analysis of

the synovial fluid demonstrating urate crystals. Frequency of consultations was more than one visit per year in 74% of cases.

Lifestyle and Dietary Advice

Table IV documents data collected on lifestyle and dietary advice. Almost all patients received lifestyle or dietary recommendations. The most frequent recommendation was the reduction of animal protein intake, followed by the consumption of at least 1.5 litres of water per day and the limitation of alcohol.

Overall, compliance to lifestyle or dietary recommendations was high (Figure 1).

Table II. Concomitant medications

Treatment	Unit	N of patients evaluated	French Cohort, %	Greek Cohort, %	Pooled percentage	OR (French vs Greek Cohort)	95% C.I.	p value
Antihypertensive treatment								
Any antihypertensives treatment	%	2607	79.7	82.9	80.4	0.8	0.6-1.0	0.0828
Diuretics	%	1889	45.3	41.0	44.4	1.1	0.9-1.4	0.1209
Sartans	%	1889	54.9	61.4	56.3	0.7	0.6-0.9	0.0192*
Other antihypertensive drugs	%	1889	45.9	32.2	42.9	1.7	1.4-2.2	< 0.0001*
Lipid-lowering treatment								
Lipid-lowering drug	%	2607	60.5	61.4	60.7	0.9	0.8-1.1	0.7002
Fenofibrate	%	1359	20.6	9.6	18.2	2.4	1.6-3.7	< 0.0001*
Statins	%	1359	79.4	91.1	81.9	0.3	0.2-0.5	< 0.0001*
Others								
Oral anti-diabetic drugs	%	2607	25.5	28.9	26.3	0.8	0.6-1.0	0.1029
Low dose aspirin (60 to 300 mg/day)	%	2607	26.1	26.0	26.1	1.0	0.8-1.2	0.9498
Hormone replacement therapy	%	2607	0.7	1.7	1.0	0.4	0.1- 0.9	0.0344*
Chemotherapy (cytotoxic drugs)	%	2607	0.5	1.2	0.7	0.4	0.1-1.1	0.0932
Cyclosporin	%	2607	0.1	0.7	0.3	0.2	0.1-0.9	0.0275*

Pharmacological Management of Gout

Data on treatment of gout attack are reported in Table V. The last gout attack occurred at 8.4 months before the inclusion visit (weighed mean).

At inclusion, 81.5% of patients were on a urate-lowering treatment. Most of these patients had been treated with allopurinol; this treatment had been interrupted for lack of reduction of SUA levels below 6 mg/dl (47%), lack of symptom relief (34%) or poor compliance (23%). At the inclusion visit, 98% of the patients were prescribed an urate-lowering treatment: 87% received febuxostat and 12% allopurinol alone. After the switch, satisfactory or very satisfactory compliance to febuxostat was recorded in 92% of the patients, versus 82% reported in patients on allopurinol (Figure 2). In the Greek cohort, the compliance levels were significantly higher in patients treated with febuxostat than with allopurinol ($p < 0.0001$). Dosages of allopurinol and febuxostat are shown in Figure 3. Of note colchicine was mainly used in France as prophylactic treatment and to treat flares, whereas NSAIDs was preferred in Greece.

Discussion

CACTUS was designed with the primary aim of investigating some characteristics of gouty patients treated in primary care in France and

Greece. While this analysis offers a unique picture of this population, we discuss here the most relevant results reported.

First, the body mass index reported at inclusion indicated that patients with gout were often overweight or obese in both countries. In addition, patients frequently presented other multiple comorbidities such as hypertension, hyperlipidemia and type 2 diabetes, in particular in Greece. Interestingly, about 10% of patients had an history of ischemic heart disease or congestive heart failure, thus, further supporting the well-recognized correlation between increased sUA levels and the risk of cardiovascular disease²⁵. In both cohorts, high rates of risk factors for the development of the disease were reported, including alcohol consumption and “non-diet” sodas.

As indicated in the recommendations of the European League Against Rheumatism (EULAR), treating physicians can use a combination of evidence from the physical examination, and/or laboratory and/or radiology data to establish the diagnosis of gout²². In the present analysis, 74% of cases of gout were initially diagnosed by the patient’s treating physician by using a combination of clinical and laboratory findings. However, the laboratory tests assessed almost exclusively sUA, while only a small proportion of physicians performed synovial fluid examination or radiology imaging to look for sclerotic erosion.

Table III. Initial diagnosis of gout and SUA levels.

	Unit	N	French value	Greek value	Pooled percentage/ weighted mean	OR/difference (French vs Greek cohort)	95% C.I.	p-value
Initial diagnosis of gout								
Years from the initial diagnosis (years)	Years	2939	5.6 ± 6.3	4 ± 5.3	5.2 ± 6.1	1.6	1.1 – 2.1	< 0.0001*
Diagnosis performed by current investigator	%	3067	77.1	60.6	73.7%	2.1	1.8 – 2.6	< 0.0001*
SUA level								
Serum uric acid at diagnosis (mg/dl)	mg/dl	2618	8.5 ± 1.2	9.2 ± 1.3	8.7 ± 1.2	-0.6	-0.7 – -0.5	< 0.0001*
Highest known sUA level (mg/dl)	mg/dl	2631	9 ± 1.3	10 ± 1.5	9.2 ± 1.4	-0.9	-1.1 – -0.8	< 0.0001*
Diagnostic information								
Presence of tophi	%	3058	10.7	12.6	11.1%	0.8	0.6 – 1.0	0.1833
Number of tophi	-	322	3.2 ± 3.3	2.7 ± 3	3.1 ± 3.2	0.5	-0.3 – 1.3	0.2173
Number of attacks during the previous 12 months	-	3043	1.9 ± 1.5	1.9 ± 1.6	1.9 ± 1.5	0.0	-0.1 – 0.1	1
Laboratory diagnostic criteria								
Hyperuricaemia	%	3060	96.8	98.4	97.1%	0.4	0.2 – 0.9	0.0285*
Steril synovial fluid sample obtained during an attack	%	2972	5.4	6.3	5.6%	0.8	0.5 – 1.2	0.3649
Presence of characteristic urate crystals in the joint fluid	%	2936	4.9	10.3	6.0%	0.4	0.3 – 0.6	< 0.0001*
Presence of a tophus proven to contain urate crystals	%	2954	4.3	6.0	4.6%	0.6	0.4 – 1.0	0.0592
Radiologic diagnostic criteria								
Signs of asymmetric effusion in a joint	%	2977	20.2	29.4	22.1%	0.6	0.5 – 0.7	< 0.0001*
Subcortical cysts with no erosion on standard radiography	%	2964	6.7	15.2	8.5%	0.4	0.3 – 0.5	< 0.0001*
Frequency of consultations								
More than one visit per year	%	2656	73.4	76.3	74%	0.8	0.6 – 1.0	0.1794

According to current recommendations^{22,27,28}, target sUA level is below 6.0 mg/dl. In the present analysis, mean of sUA at diagnosis was 8.7 mg/dL, therefore, prompting the prescription of urate-lowering therapy.

The vast majority of the physicians selected allopurinol monotherapy as the initial long-term treatment, regardless of the levels of sUA. However, poor patient compliance to allopurinol was reported in about one out of four pa-

tients, and treatment with this molecule was frequently discontinued due to persisting high levels of sUA.

A large proportion of the patients switched from allopurinol monotherapy to febuxostat monotherapy at the inclusion visit. This indicates a change in the clinical attitude of the physicians; in addition, better compliance to febuxostat treatment was recorded, especially reported in the Greek cohort. However, information on the out-

Table IV. Lifestyle and dietary advice, and related compliance.

	Unit	N	French value	Greek value	Pooled percentage	OR (French vs Greek cohort)	95% C.I.	p-value
Life-style / dietary recommendations given	%	3071	97.5	98.6	97.7%	0.56	0.28-1.14	0.1047
Reduction of animal protein intake	%	2997	93.8	98.7	94.8%	0.20	0.10-0.40	< 0.0001*
Consumption of at least 1.5 liters of water per day	%	2997	75.7	92.1	79.1%	0.27	0.20-0.36	< 0.0001*
Limitation of alcohol consumption	%	2997	76.4	86.3	78.4%	0.51	0.4-0.66	< 0.0001*
Regular physical exercise	%	2997	67.8	70.7	68.4%	0.87	0.72-1.06	0.1648
Low-calories diet	%	2997	65.9	69.8	66.7%	0.84	0.69-1.02	0.0705
Limitation of saturated fats consumption	%	2997	56.1	74	59.8%	0.45	0.37-0.55	< 0.0001*
Limitation of beer consumption	%	2997	49.8	79.1	55.9%	0.26	0.21- 0.32	< 0.0001*
Limitation of sweet consumption	%	2997	50.5	65.9	53.7%	0.53	0.44-0.63	< 0.0001*
Satisfactory compliance to recommendations	%	2909	49.7	62.8	52.3%	0.59	0.48- 0.71	< 0.0001*
Limitation of salt consumption	%	2997	44.1	70.4	49.5%	0.33	0.27- 0.40	< 0.0001*
Limitation of soft drink consumption	%	2997	40.3	71.4	46.8%	0.27	0.22-0.33	< 0.0001*
Stopping smoking	%	2997	0.0	1	0.2%	0.09	0.01-0.84	0.0074*
Weight decrease	%	2997	0.1	0.5	0.2%	0.13	0.03-0.52	0.0007*

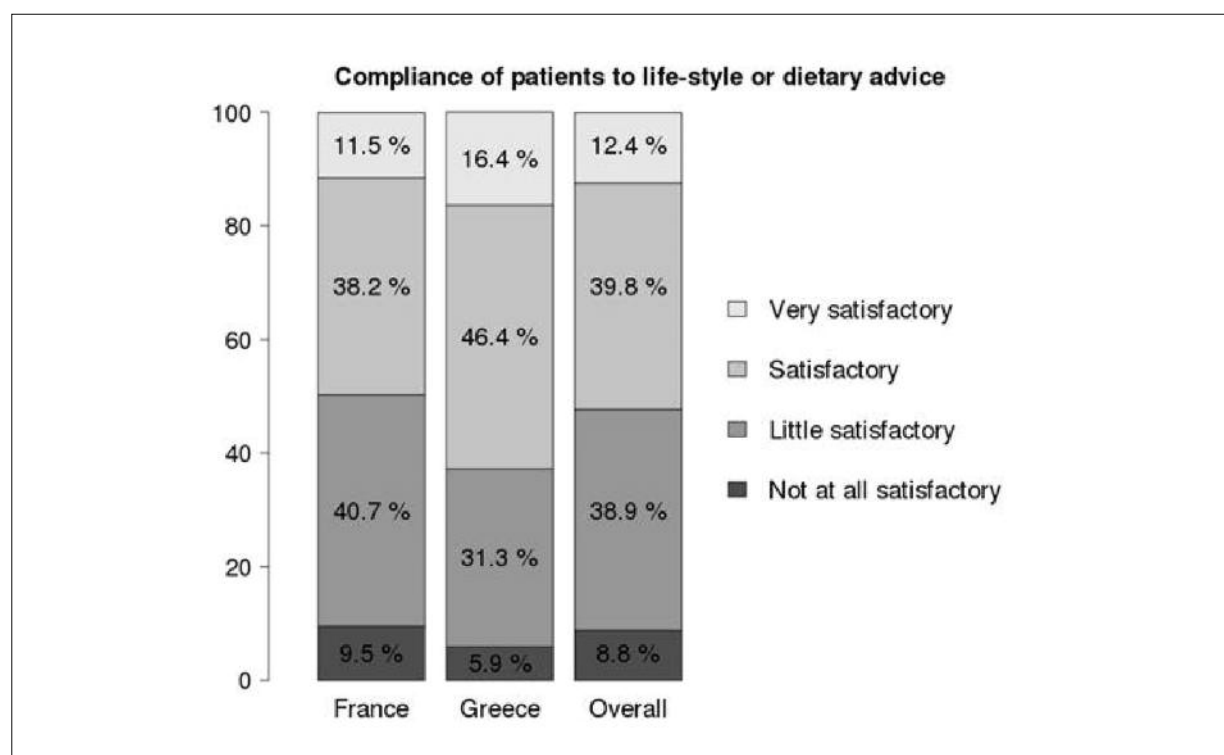

Figure 1. Compliance of patients to lifestyle and dietary advice according to the investigators in the French and Greek studies.

Table V. Treatment of gout.

	Unit	N	French value	Greek value	Pooled percentage/ weighted mean	OR/difference (French vs Greek cohort)	95% C.I.	p-value
Most recent episode of gout								
Time since the most recent gout attack	Months	2956	9.5 ± 24.2	6.9 ± 15	8.4 ± 22.6	2.6	1.0-4.1	0.001*
Colchicine	%	2990	92.1	42.4	81.9%	15.8	12.7-19.7	< 0.0001*
NSAIDs	%	2990	36.4	72.4	43.8%	0.2	0.1-0.2	< 0.0001*
Corticosteroids	%	2990	1.1	8.9	2.7%	0.1	0.1-0.2	< 0.0001*
Urate lowering therapy								
At least one previous long-term treatment	%	3032	80.7	84.3	81.5%			
Current treatment prescribed at the inclusion visit (Allopurinol or febuxostat)	%	3065	98.2	99.5	98.5%	0.2	0.1- 0.8	0.0195*
Allopurinol	%	3012	11.3	12.9	11.7%	0.8	0.6-1.1	0.2617
Febuxostat	%	3012	87.3	87.2	87.3%	1.0	0.7-1.3	0.955
Allopurinol + Febuxostat	%	3012	1.0	0.2	0.9%	6.5	0.8-48.1	0.0345*
Treatment prescribed by the current investigator	%	2915	95.9	90.6	94.9%	2.4	1.7-3.4	< 0.0001*
Previous allopurinol treatment and reasons for discontinuation								
Previous allopurinol monotherapy	%	2287	99.1	90.8	97.3%	10.5	6.0-18.6	< 0.0001*
Lack of symptom relief	%	1974	33.0	39	34.3%	0.7	0.6- 0.9	0.0198*
Lack of reduction of SUA	%	1974	45.7	53.8	47.5%	0.7	0.5- 0.8	0.0028*
Adverse events	%	1974	6.6	3.0	5.8%	2.3	1.3- 4.2	0.0037*
Poor patient compliance	%	1974	25.7	13.4	22.9%	2.2	1.6-2.9	< 0.0001*
Other reasons	%	1974	3.6	3.4	3.6%	1.0	0.6-1.9	0.8184
Previous febuxostat treatment and reasons for discontinuation								
Previous Febuxostat monotherapy	%	1099	23.0	2.2	13.7%	13.0	6.9-24.3	< 0.0001*
Lack of clinical efficacy	%	24	11.8	7.1	10.4%	1.7	0.1-43.9	0.7362
Lack of clinical efficacy in relation to sUA levels	%	24	35.3	42.9	37.5%	0.7	0.1-4.3	0.7279
Adverse events	%	24	11.8	42.9	20.8%	0.1	0.1-1.4	0.0882
Poor patient compliance	%	24	23.5	42.9	29.2%	0.4	0.1-2.6	0.3437
Other reasons	%	24	17.6	14.3	16.7%	1.2	0.1-1.5	0.8408
Prophylactic treatment								
Any prophylactic treatment	%	3017	72.0	40.6	65.6%	3.7	3.1-4.5	< 0.0001*
Colchicine	%	1963	97.0	57.9	92%	23.6	16.2- 34.3	< 0.0001*
NSAID	%	1963	5.8	47.6	11.2%	0.1	0.1- 0.2	< 0.0001*
Corticosteroids	%	1963	0.2	2.0	0.4%	0.1	0.1-0.3	< 0.0001*
Other prophylactic treatment	%	1963	0.8	0.8	0.8%	0.9	0.2-4.2	0.954

comes obtained with the administration of febuxostat were not collected. In parallel to the long-term treatment, the majority of patients received concomitant prophylactic treatment, which is known to contribute to the prevention of new

gout attacks and to the reduction of the number and the severity of gout episodes²⁹.

Non-pharmaceutical recommendations apart from the administration of pharmaceutical treatment are also useful in these patients according

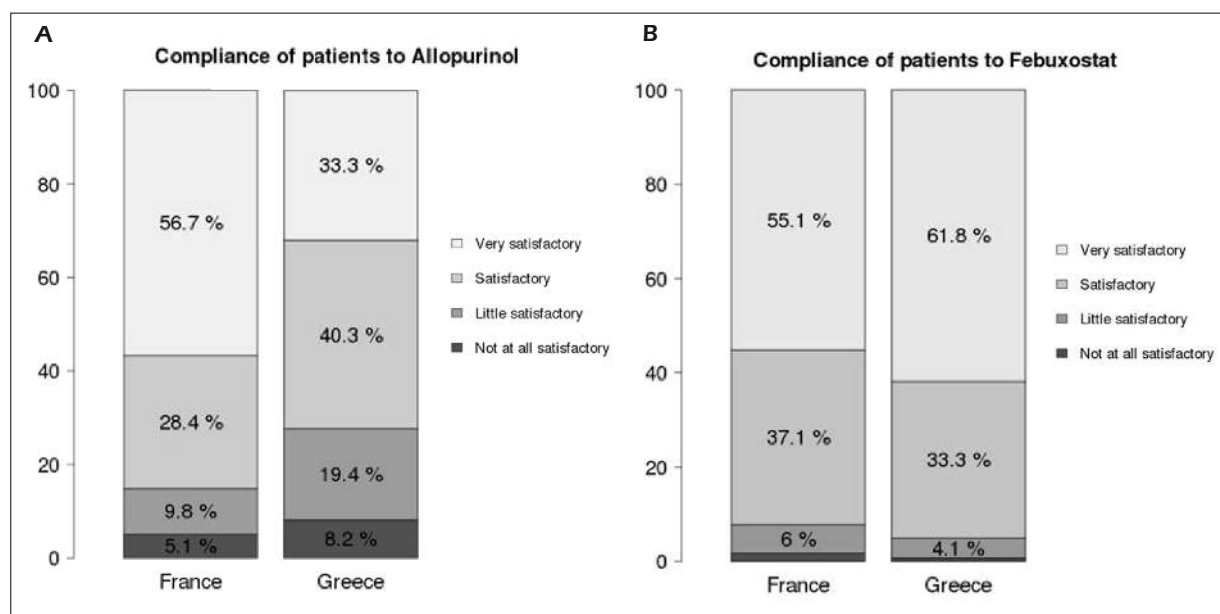


Figure 2. Compliance of the patients to allopurinol (A) and febuxostat (B).

to current recommendations^{22,27,28}. Overall, physicians found patient compliance to these recommendations satisfactory or very satisfactory: appropriate lifestyle and dietary intervention may therefore corroborate, at least partly, the efficacy of long-term urate lowering treatment in reducing hyperuricaemia, in line with a previous experience which reported increased adherence with appropriate patients' education^{25,30}.

Conclusions

Even if with all the limitations of any registry analysis, CACTUS provides an overview of characteristics of gouty patients and gout management. Education of patients by healthcare providers seem to be a prerequisite to optimize the management of gout, a condition which remains poorly managed.

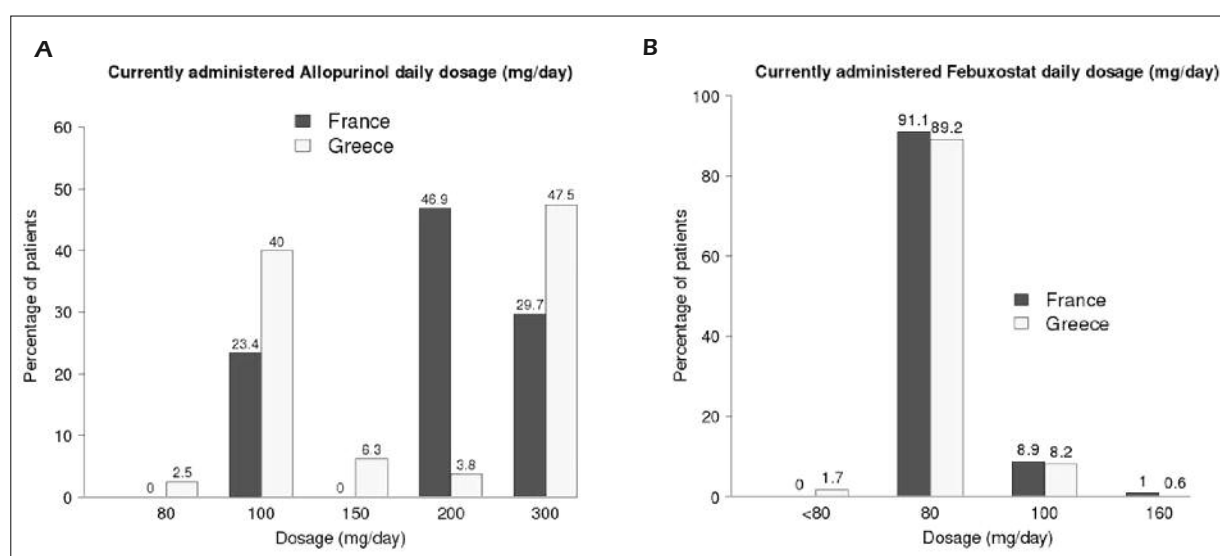


Figure 3. Allopurinol (A) and febuxostat (A)* dosage (mean daily dosage).

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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