Introduction

Gout is a chronic disease caused by the precipitation of monosodium urate crystals in the joints, leading to inflammation, pain and joint destruction [1, 2]. Worldwide, the incidence of the disease has increased substantially over recent decades [3–7]. Gout is more prevalent among men older than 30 years and is becoming more common in post-menopausal women [3, 5].

Although the pathogenesis of gout is well established, guidelines are lacking for proper diagnosis and the setting of therapeutic targets [6, 8–10]. Therapy with allopurinol is commonly utilized on a chronic basis in order to prevent further attacks and to maintain a normal uric acid level [8, 11–13]. Nonetheless, and despite the high prevalence of gouty arthritis, many patients do not adhere to long-term therapy and hence suffer from recurrent attacks [14, 15]. A previous study from the USA has demonstrated that more than half of the patients do not adhere to allopurinol therapy [16].

The aim of this study was to assess rates of adherence and persistence with allopurinol therapy in Israel and to identify the risk factors associated with low compliance to the drug in order to set a basis for intervention programmes.
Methods

We conducted a retrospective cohort study among the members of Maccabi Healthcare Services (MHS), a 2-million enrollee (in 2012) health maintenance organization (HMO) operating in Israel. According to the Israeli National Health Insurance Act, MHS may not bar any citizen who wishes to join it, and therefore every section in the Israeli population is represented in MHS. According to the most recent report of Israel National Insurance [17], the mean age and proportion of women among MHS members (31.0 years, 48.6%) is similar to the general population (32.4 years, 48.9%). All data were obtained from MHS automated databases that have previously been described [17] and were used to elicit information on all dispensed community prescriptions, hospital discharge data and biochemistry results using a unique nine-digit national identification number. Research ethics approval was obtained from the Assuta Medical Center institutional review board.

Study outcomes

Incident cases of gout were defined by the date of first diagnostic codes associated with gout with allopurinol therapy as identified by the International Classification of Diseases, 9th revision [(ICD-9) code 714.x] during the study follow-up period. Patients age 25 years or older with the diagnosis of gout treated with allopurinol were identified over a 7-year period (2002–2009) by the MHS database. Diagnosis of gout in primary care is usually based only on clinical signs and symptoms and often does not include SF analysis for the presence of MSU crystals [18, 19]. As a consequence, the validity of family physician diagnosis of acute gouty arthritis was previously reported to be suboptimal. Therefore we have included only patients diagnosed with gout by rheumatologists.

Measurement of adherence and persistence with allopurinol

Persistence with allopurinol was based on the continuation of drug use for an overall duration of drug therapy. Discontinuation of allopurinol was defined as the point at which a patient would have had an insufficient supply of drug to cover 80% of follow-up days plus a fixed grace period of 30 days afterwards [20].

Adherence with medication refers to the extent of drug use during the period of persistence, which was estimated by mean proportion of days covered (PDC). Following previous studies [17, 21], we calculated the mean PDC by dividing the quantity of allopurinol dispensed by the total time interval from index date to drug cessation, death, leaving MHS or 31 December 2009, whichever occurred first. As presented in previous publications regarding standard of compliance to therapy, drug adherence >80% was considered to be high, while between 20% and 80% was medium and <20% was considered to be poor drug adherence [17, 19, 22, 23].

Other study variables

We collected data on demographic variables at the index date that have been previously reported as related to compliance with allopurinol therapy [13] or with other medications in MHS, including age, sex, marital status, place of residency and years of stay in Israel (for new immigrants). Socioeconomic level was categorized into quintiles according to the poverty index of the member’s enumeration area, as defined by the 1995 national census. The poverty index is based on several parameters, including household income, educational qualifications, crowding, material conditions and car ownership [24]. Chronic comorbidity has been associated with better adherence with allopurinol [16]. Therefore study subjects’ electronic medical records were reviewed for a diagnosis of chronic conditions such as chronic obstructive pulmonary disease (COPD), psychotic disease, morbid obesity, Alzheimer’s disease and asthma defined by ICD-9 codes. Diabetes mellitus patients were identified by using the MHS computerized diabetes mellitus patient registry [22]. Information on cancer history was provided by the Israel National Cancer Registry (INCR), which has collected information of diagnosed cancer cases from all medical institutions in Israel since 1960.

Information on health services utilization, such as the number of hospitalizations in general hospitals, visits to outpatient clinics and filled prescriptions of anti-hypertensive drugs and diuretics, were based on data collected for the year prior to the index date.

Statistical analysis

Chi-square test for categorical variables and Kruskal–Wallis test for continuous variables were performed to determine significant differences in baseline characteristics and PDC levels between primary and secondary prevention cohorts. Cox regression with years of follow-up as the time scale was used to estimate hazard ratio (HR) and 95% CI [25]. Each participant was followed from the first purchase of allopurinol to drug cessation, leaving MHS or 31 December 2009, whichever occurred first. The maximum follow-up was approximately 10 years. To examine a potential prevalence incidence bias, we excluded patients with less than 1 year of follow-up. In addition, we conducted sensitivity analyses limited to patients with at least 5 years of follow-up.

The full multivariable model included the following baseline values: age at baseline (in 1-year intervals), gender, marital status, nationality, socioeconomic level, presence of chronic co-morbidity and utilization of health services. Tests for trend of ordinal variables were based on the category median values. Analyses were stratified by age categories and sex. A chi-square test was performed to assess heterogeneity.

The patients were assessed for the degree of compliance by the PDC by allopurinol prescriptions provided by the family physician. Demographics including age, sex, marital and socioeconomic status, smoking history, concomitant chronic diseases (hypertension, diabetes and cardiovascular disease), BMI (categorized
The median number of MHS members during the study period was more than 1.6 million, with persons aged 18 years or older accounting for 66% of the population. A total of 7644 patients were identified by prescription history and were predominantly men (72%). During the study follow-up, 962 patients (12.6%) passed away and 132 (1.7%) left MHS. In 2008 alone, the incidence of gout was 2.6 new cases per 1000. The male:female ratio was 10:1 in the younger group (45–65 years) and 3.5:1 in the elderly group (≥85 years) (Fig. 1). The annual incidence rate of gout increased substantially both for men and women after the age of 54 years. At the age of 85, 36.2% of elderly men had gout compared with 10.1% of women (Fig. 1).

Rates of compliance were inversely related to socio-economic level. Comorbidities were recorded in a high percentage of the patients: 42.8% had a cardiac disorder, 13.7% had a previous myocardial infarction, 32.4% were diabetic, 18.7% had a history of malignant conditions, 81.6% had hypertension, 8% had osteoporosis and 2% were on haemodialysis.

Adherence and persistence with allopurinol therapy

The vast majority of patients were non-adherent to medical therapy with allopurinol. A total of 1331 patients (17% of the total study population) had a PDC of ≥80%, while 2745 patients (36%) were partial adherers (20% < PDC < 80%) and 3568 (47%) adhered poorly (PDC < 20%). Higher PDC levels to therapy were recorded among men compared with women and steadily improved with age (Fig. 2). Analysis of the adjusted odds ratios (ORs) for non-adherence by age group demonstrated that the highest degree of non-adherence occurs in the age group 45–54 years, declining with age.

The median time to discontinuation of therapy in men compared with women was 358 days and 379 days, respectively (Fig. 3). Persistence with allopurinol was associated with the number of doctor visits, being married and belonging to a higher socioeconomic status. Patients with cardiovascular risk factors were more likely to demonstrate high adherence rates compared with those with other chronic diseases such as cancer or dialysis.

Increased uric acid levels were associated with a lower risk of non-compliance (OR = 0.996 per 1 mg/dl; 95% CI 0.992, 0.998). In univariate and multivariable analyses, women (45–65 years), when compared with the older age group and men, were significantly more prone to be non-compliant. Non-married individuals and those of a low socioeconomic status were also more likely to become non-compliant. These results were confirmed when analyses were limited to 32% of the study sample (n = 2471) who were evaluated by doctor visits. Compliance was better achieved among those with chronic illnesses, particularly cardiovascular disease (Table 1).

**Discussion**

In the present population-based study of patients with gout, we found relatively poor adherence and persistence rates with allopurinol therapy. According to our results, approximately only one out of six gout patients persisted with allopurinol therapy; the average time to therapy discontinuation was approximately 1 year.
In a retrospective claims-based analysis, Riedel et al. [29] found similar [16] or better [13] adherence with allopurinol among women, our study showed that women were more often non-compliers when compared with men. However, a more recent study using medical and pharmacy claims for more than 55 million patients from more than 90 US managed care health plans indicates much higher allopurinol use among men. One possible reason for the observed gender differences in adherence may be the increased incidence of flares reported over time (60%) among women with gout compared with 10% among male patients [30]. High flare rates may contribute to a loss of confidence in the benefit of the medication and may lead to subsequent poor adherence. The clear strength of this study originates from its size; the results reflect the entire relevant population of the second largest HMO in Israel. In this study we evaluated more than 7000 patients over a 7-year period, providing a strong statistical basis for analysis and conclusions regarding the medical characteristics of compliance and adherence to allopurinol therapy and the necessary measures that need to be taken.

Naturally such a study also has caveats. As in any database study, we could not validate the diagnosis of gout; however, the use of allopurinol highly increases the likelihood and validity of the diagnosis of gout. We determined compliance parameters on the rates of prescriptions actually dispensed, assuming that if a patient purchased the medication he or she actually used it. Given the chronic nature of gout, we believe that only a minute fraction of patients stopped taking allopurinol due to their physicians’ recommendations.

In conclusion, to the best of our knowledge this is the first study in Israel investigating the patterns of compliance in a large population of patients with gout treated with allopurinol. This study emphasizes the need to inquire and monitor therapy adherence in patients with a chronic disease in general and in gout in particular. It is imperative to identify the population at risk and launch interventional actions for prevention of non-compliance addressing women aged 55–64 years old, unmarried patients, low socioeconomic status individuals and young patients who suffer from gout without other concomitant diseases. The reason for non-compliance is multifactorial and may relate to the cost of the subsidized medication, level of education or the ease of access to the clinic and prescribing physician. It is important to improve communication and to address patients with regard to medication compliance as an integral part of the clinical interaction.

An encouraging indication that such goals are attainable comes from a recent predominantly nurse-led intervention that included education, lifestyle advice and urate-lowering therapy in patients with ongoing attacks of gout. This initiative succeeded in achieving treatment targets in more than 9 out of 10 patients during the year it was conducted [31]. Physicians should be aware of the problematic nature of adherence and compliance with allopurinol; inquiry, documentation and reaching out to those who are prone to non-compliance is pertinent.
Most patients with gout in MHS, Israel, discontinue allopurinol following the first year of therapy. In Israel, single women of middle age, low socioeconomic status and lower body weight with gout are more likely to discontinue allopurinol therapy. Better compliance with allopurinol therapy is achieved among gout patients in Israel who have other comorbidities.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**

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