Durg Corner

Effectiveness of Regular Monitoring on Adherence to Urate – Lowering Therapy and Its Effect on Serum Uric Acid Levels in Indian Subjects — A Retrospective Analysis

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Purpose : To evaluate the effect of continuous monitoring on treatment compliance and Serum Uric Acid (SUA)levels in Indian subjects enrolled in a patient support program.

Methods : SUA level data of subjects aged ≥18 years attending the program, collected between July 2019 and October 2019, were considered for this retrospective analysis. Primary study variables were mean changes in SUA levels after 60 and 90 days of monitoring.The secondary study variables includedthe proportion of subjects on urate-Lowering Therapy (ULT) on Days 30, 60 and 90.

Results : Of 2108 subjects with hyperuricemia, SUA level data up to 90-day follow-up pointwere available for 1573 subjects. Compared to the Day 0 mean levels of 7.8 mg/dL, SUA levels declined significantly (*P*<0.0001) by 1.1 and 2.0 mg/dL at Days 60 and 90, respectively. In the ≥18—≤30 years age group,this decline was by 1.4 and 2.1mg/dL(*P*<0.0001) at Days 60 and 90, respectively. Similarly, in the >30—≤40, >50—≤65 and >65 years age groups, the decline was by 1.1 and 2.0 mg/dL (*P*<0.0001) on Days 60 and 90, respectively. In the >40—≤50 years age group, the SUA values declined by 1.1 and 1.9 mg/dL(*P*<0.0001) on Days 60 and 90, respectively. Treatment compliance was 100% at Day 30 and 89.0% and 74.6% at Days 60 and 90, respectively, with 83.9% of subjects achieving target SUA levels at Day 90.

Conclusion : Clinician-guided intervention led to significant improvements in adherence to ULT and achievement of SUA goals in Indian subjects.

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Key words **: Hyperuricemia, Monitoring, Serum uric acid, Treatment compliance.**

Hyperuricemia is a metabolic condition characterized by elevated Serum Uric Acid (SUA) levels[1,2]. Evidence suggests that hyperuricemia is the predecessor of cardiovascular diseases and closely related vascular diseases such as vascular dementia, preeclampsia, cerebrovascular disease, and renal disease[1,3,4]. In India, the overall prevalence rate of hyperuricemia is reported to be between 24.66%[5]—25.8%[6], with higher preponderance in males and patients with other metabolic comorbidities like hypertension and/or type 2 diabetes[5,6].

Subjects with hyperuricemia typically have SUA levels >6.0 mg/dL in women and >7.0 mg/dL in men[1,2]. There has been a growing acknowledgment that hyperuricemia may be a strong independent predictor of hypertension and may actually be causative[7]. The Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study showed that for every 1 mg/dL increase in SUA level, the risk of new-onset home and ambulatory hypertension increased by 34% and 29%, respectively[8]. Elevated SUA concentration has been associated with a significantly increased risk of heart failure (HF) when compared to adults with normal SUA[9]. A meta-analysis by Kim *et al* found a 12% increase in mortality with every 1 mg/dL increase in SUA in a person with Coronary Heart Disease (CHD)[10]. Moreover, elevated SUA levels increase the risk of HF and cardiovascular-related hospitalization and contribute to poor long-term survival and adverse outcomes in patients with HF[11-13]. Hyperuricemia also causes slow decline in kidney function[14]. Hyperuricemia is both a predictor of onset and a modulator of progression for both acute kidney injury

Editor's Comment :

- In a retrospective analysis of 2108 adult Indian subjects on Urate-lowering Therapy (ULT) attending a patient support program,effect of hyperuricemia monitoring on treatment compliance and Serum Uric Acid (SUA) levels was analyzed
- A decline in SUA levels was observed in the overall population and in subjects of all age groups following 60 and 90 days of treatment with ULT
- While mean SUA levels at baseline were lower in female subjects relative to male subjects, the magnitude of decline at 60 and 90 days was also lower in female subjects
- Clinician-guided intervention via regular monitoring helped achieve high rates of treatment compliance and attainment of target SUA levels

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and chronic kidney disease (CKD)[14]. Large scale trials including the German Chronic Kidney Disease (GCKD) study[15] and NHANES[16] showed that the age-standardized prevalence of hyperuricemia and gout increases with the decline in Glomerular Filtration Rate (GFR).

The disease burden associated with hyperuricemia and its associated comorbidities continues to increase[17]. Despite the availability of several drugs as urate-lowering therapy (ULT) with or without cardiac and renal benefits,adherence to therapy remains poor[18,19]. Therefore, implementing potentially effective interventions is crucial[20]. Healthcare provider-led continuous monitoring of patients on ULT could facilitate improved adherence to treatment and optimal control of SUA levels. Here, we present retrospective analysis of data collected from Indian subjects attending a patient support program for SUA monitoring and ULT adherence conducted across different cities in India between July and October 2019.

Materials and Methods

Study design and population :

For this retrospective analysis, SUA level data of Indian subjects aged ≥18 years on ULT who attended a patient support program were collected between July 2019 and October 2019. Subject records with incomplete information were excluded. The data were collated from central laboratory information management systems of RxPONT India Private Limited, Bangalore, India. Subjects' demographic details and results of the SUA tests performed on Day 0, 30, 60, and 90 were analyzed. Hyperuricemia was defined as SUA concentration of >6.0 mg/dL for women and >7.0 mg/dL for men[1,2].

The study was conducted in conformity with the principles of the Declaration of Helsinki, International Council for Harmonization-Good Clinical Practices (ICH-GCP) guidelines, Indian Council of Medical Research, Indian GCP guidelines, and as per the approved protocol. Data analysis was initiated after approval of the study protocol by the independent ethics committee. Given the retrospective nature of data collection, informed consent was not required. Subject confidentiality was maintained during the data entry and analysis process.

Study variables :

The primary variable was mean change in SUA levels after 60 and 90days of monitoring.The secondary variables were proportion of subjects on ULT therapy on Days 30, 60, and 90, overalland by age groups ≥18-≤30, >30-≤40, >40-≤50, >50-≤65, and >65 years; overall mean change in SUA levels after 60 and 90 days of monitoring; and mean change by sex and age groups ≥18-≤30, >30 -≤40, >40-≤50, >50-≤65, and >65 years.

Statistical analysis :

All the subjects with SUA level data up to the 90-day follow-up point (per protocol [PP] set) were included in this retrospective analysis. Treatment compliance was assessed in the intention-to-treat (ITT) population consisting of all subjects with ≥1 SUA level reading. Qualitative and quantitative variables are presented using descriptive statistics. Quantitative variables were evaluated using a paired *t*test at the 5% level of significance.

Results

Disposition and baseline characteristics :

A total of 2950 subjects (1756 males and 1194 females) were enrolled in the patient support program, out of which 2108 (71.5%) had hyperuricemia and were considered for analysis. After excluding subjects with missing data, 1573 subjects (668 males and 905 females) with SUA level data up to 90 days were included in the analysis. Demographic and baseline characteristics of subjects are summarized in Table 1.

Change in SUA levels

Mean overall change in SUA levels and change by age groups are shown in Table 2.

Compared to the Day 0 mean (SD) levels of 7.8 (1.1) mg/dL,SUA levels declined significantly (P<0.0001) by 14.1% at Day 60, and further by 25.6% at Day 90. The trend in the decline of SUA levels was evident across all age groups. In the ≥18—≤30 years group, mean (SD)SUA levels on Days 60 and 90reduced significantly (P<0.0001) by 17.7% and 26.6%, respectively, compared to Day 0 levels of 7.9 (1.1) mg/dL. Likewise, the mean (SD) SUA levels at Day 0 were 7.8 (1.2) mg/dL, in the >30—≤40 years group, which declined significantly (P<0.0001) by 14.1% on Day 60, and further by 25.6% on Day 90. Among the subjects in the >40-≤50 years group, compared to Day 0 levels of 7.7 (1.1) mg/dL, SUA levels declined significantly (P<0.0001) by 14.3% and 24.7% on Days 60 and 90, respectively. A significant decline in SUA levels also resonated in older subjects (≥50 years). In these subjects, mean SUA levels declined significantly (P<0.0001) by 14.1% and 25.6% on Days 60 and 90, respectively.

The significant reduction in SUA levels echoed in male and female subjects across all age groups (Table 3). In male subjects,SUA levels on Days 60and 90

Table 1 — *Baseline characteristics*

	ITT (N = 2108)[#]	PP (N = 1573)
Sex, n (%) :		
Males	935 (44.4)	668 (42.5)
Females	1173 (55.6)	905 (57.5)
Age (years) :		
Mean (SD)	43.6 (12.4)	43.8 (12.4)
Median (Range)	42.0 (21.0-84.0)	42.0 (21.0-84.0)
Age Group n (%) :		
≥18-≤30 years	339 (16.1)	241 (15.3)
>30-≤40 years	604 (28.7)	459 (29.2)
>40-≤50 years	570 (27.0)	430 (27.3)
>50-≤65 years	504 (23.9)	371 (23.6)
>65 years	91 (4.3)	72 (4.6)

[#]Male subjects with SUA levels >7 mg/dL and female subjects with SUA levels >6 mg/dL; SD= standard deviation

reduced significantly (P<0.0001) by 18.3% and 28.0%, respectively. Similarly, in female subjects, SUA levels declined significantly (P<0.0001) by 12.0% and 22.7% on Days 60 and 90, respectively.

Male subjects in the ≥18—≤30 years group showed a significant decline (P<0.0001) of 21.7% and 30.1% on Days 60 and 90, respectively. Female subjects in the same age groups showed a relatively lower, yet significant (P<0.0001), decline of 12.0% and 24.0% on Days 60 and 90, respectively. In male subjects aged >30—≤40 years, mean SUA levels reduced significantly (P<0.0001) by 18.1% on Day 60 and by 28.9% on Day 90. Likewise, in female subjects of the same age group, mean SUA levels declined significantly (P<0.0001) by 12.0% and 22.7% on Days 60 and 90, respectively. In the >40-≤50 years age group, significant (P<0.0001) decreases of 18.3% and 29.3% were observed on Days 60 and 90, respectively. For the same age groups, female subjectsshowed a lower, yet significant decline (P<0.0001) of 10.8% and 21.6% on Days 60 and 90, respectively.

A similar trend was observed in the >50—≤65 years age group,with significant (P<0.0001) decreases of 16.0% and 27.2% for malesand decreases of 10.7% and 22.7% for females, on Days 60 and 90, respectively. In the >65 years age group, as well, male subjects showed a significant (P<0.0001) decline of 18.7% on Day 60 and 27.2% on Day 90, whereas female subjects showed a comparatively lower decline of 10.5% (P = 0018) on Day 60 and of 25.0% on Day 90.

Treatment compliance and attainment of SUA target levels :

Adherence to ULT was 100% on Day 30 and 89.0% and 74.6% on Days 60 and 90, respectively (Fig 1). Compliance on Days 60 and 90 was highest in the >65 years age group (91.2% and 79.1%, respectively), followed by the >40-≤50 years group (89.8% and

Table 2 — *Mean change in SUA levels overall and by age*

Age Groups (n)	Day 0 Mean (SD)	Day 60 Mean (SD)	Difference (95% CI)	*P value*	Day 90 Mean (SD)	Difference (95% CI)	*P value*
Overall (1573)	7.8 (1.1)	6.7 (1.2)	–1.1 (–1.2, –1.0)	<0.0001	5.8 (0.6)	–2.0 (–2.0, –1.9)	<0.0001
≥18—≤30 years (241)	7.9 (1.1)	6.5 (1.1)	–1.4 (–1.6, –1.2)	<0.0001	5.8 (0.6)	–2.1 (–2.3, –2.0)	<0.0001
>30—≤40 years (459)	7.8 (1.2)	6.7 (1.1)	–1.1 (–1.2, –0.9)	<0.0001	5.8 (0.6)	–2.0 (–2.1, –1.9)	<0.0001
>40—≤50 years (430)	7.7 (1.1)	6.6 (1.2)	–1.1 (–1.2, –0.9)	<0.0001	5.8 (0.6)	–1.9 (–2.0, –1.8)	<0.0001
>50—≤65years (371)	7.8 (1.1)	6.7 (1.2)	–1.1 (–1.2, –0.9)	<0.0001	5.8 (0.6)	–2.0 (–2.1, –1.8)	<0.0001
>65 years (72)	7.8 (1.3)	6.7 (1.3)	–1.1 (–1.6, –0.7)	<0.0001	5.8 (0.6)	–2.0 (–2.3, –1.7)	<0.0001

P values by paired *t* testCI, confidence interval; SD, standard deviation; SUA, serum uric acid

Table 3 — *Mean Change in SUA Levels by Sex and Age*

Age Groups (n)	Day 0 Mean (SD)	Day 60 Mean (SD)	Difference (95% CI)	*P value*[a]	Day 90 Mean (SD)	Difference (95% CI)	*P value*[a]
Male Subjects :							
Overall (668)	8.2 (1.0)	6.7 (1.2)	–1.5(–1.6, –1.4)	<0.0001	5.9 (0.7)	–2.3 (–2.4, –2.3)	<0.0001
≥18—≤30 years (125)	8.3 (1.0)	6.5 (1.2)	–1.8 (–2.0, –1.5)	<0.0001	5.8 (0.7)	–2.5 (–2.6, –2.3)	<0.0001
>30—≤40 years (190)	8.3 (1.1)	6.8 (1.2)	–1.5(–1.7, –1.3)	<0.0001	5.9 (0.7)	–2.4 (–2.5, –2.2)	<0.0001
>40—≤50 years (158)	8.2 (1.0)	6.7 (1.3)	–1.5(–1.8, –1.3)	<0.0001	5.8 (0.6)	–2.4 (–2.6, –2.2)	<0.0001
>50—≤65years (163)	8.1 (1.0)	6.8 (1.2)	–1.3(–1.6, –1.1)	<0.0001	5.9 (0.7)	–2.2 (–2.4, –2.0)	<0.0001
>65 years (32)	8.1 (1.1)	6.6 (1.1)	–1.5(–2.0, –0.9)	<0.0001	5.9 (0.7)	–2.2 (–2.6, –1.8)	<0.0001
Female Subjects :							
Overall (905)	7.5 (1.1)	6.6 (1.2)	–0.9 (–0.9, –0.7)	<0.0001	5.8 (0.5)	–1.7 (–1.8, –1.6)	<0.0001
≥18—≤30 years (116)	7.5 (1.1)	6.6 (1.1)	–0.9 (–1.2, –0.7)	<0.0001	5.7 (0.5)	–1.8 (–2.0, –1.6)	<0.0001
>30—≤40 years (269)	7.5 (1.1)	6.6 (1.1)	–0.9 (–1.0, –0.6)	<0.0001	5.8 (0.5)	–1.7 (–1.8, –1.6)	<0.0001
>40—≤50 years(272)	7.4 (1.1)	6.6 (1.1)	–0.8 (–1.0, –0.7)	<0.0001	5.8 (0.6)	–1.6 (–1.7, –1.5)	<0.0001
>50—≤65years(208)	7.5 (1.2)	6.7 (1.3)	–0.8 (–1.0, –0.5)	<0.0001	5.8 (0.5)	–1.7 (–1.9, –1.6)	<0.0001
>65 years(40)	7.6 (1.4)	6.8 (1.4)	–0.8 (–1.5, –0.1)	0.018	5.7 (0.4)	–1.9 (–2.3, –1.4)	<0.0001

P values by paired *t* test; CI= confidence interval; SD = standard deviation; SUA = serum uric acid

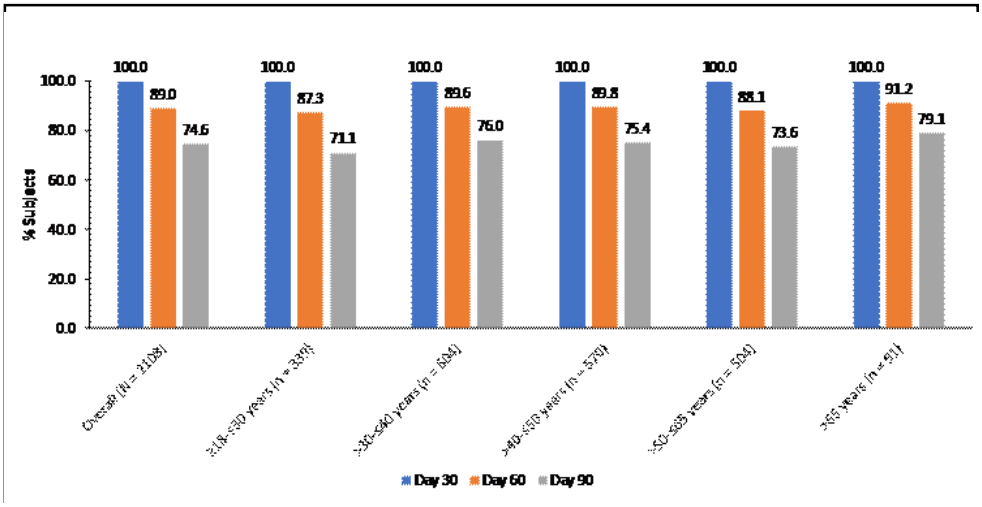

Fig 1 — Proportion of subjects on urate-lowering therapy on Days 30, 60 and 90 (ITT population)
ITT = intention-to-treat

75.4%, respectively) and the >30-≤40 years group (89.6% and 76.0%, respectively). Overall, 83.9% of subjects achieved target SUA levels (≤7mg/dL for males and ≤6mg/dL for females)by Day 90 (94.0% male subjects and 76.5% female subjects (Fig 2).

Discussion

Despite the well-known detrimental effects of elevated SUA levels, measuring of SUA levels is not a routine clinical practice[21]. Clinical and laboratory evaluations are generally conducted on the presentation of musculoskeletal pains or evident gout flare-ups[21].

The present retrospective, analysis evaluated the impact of continuous monitoring and follow-up on adherence to ULT and its effect on SUA levels in Indian subjects. The study findings indicate that elevated SUA levels are highest in the >30-≤40 years age group (28.7%), followed by >40-≤50 years (27.0%), and >50-≤65 years (23.9%) age groups; values are also higher in females than in males.

Baseline mean SUA level of 7.8 (1.1) mg/dLin our study is comparatively higher than that reported in other Indian studies. In a study of hypertensive and normotensive volunteers (N=50 each, SUA ≥6.8 mg/dL), Raina et al reported mean SUA levels of 5.5(1.7) mg/dL and 4.9(1.1) mg/dL, respectively[22]. A study involving healthy Assamese participants and a rural population-based study from West Bengal reported levels of 5.5 (1.4)[23] mg/dLand 4.2 (1.3) mg/dL[24], respectively.In contrast, a recent study evaluating SUA levels between rural and urban populations found mean SUA levels of 8.1 (0.6) mg/dL and 9.3 (1.1) mg/dL, respectively[25].

Non adherence to recommendations of physicians or healthcare providers is a crucial barrier to effective medical treatment, and when preventive or treatment regimens are complex and/or require changes in current habits and lifestyle, non-compliance can be as high as 70%[26]. Moreover, adherence to ULT is also complicated by the often asymptomatic nature of hyperuricemia. Despite multiple guidelines for the management of hyperuricemia, therapy is rarely monitored and treatment targets are

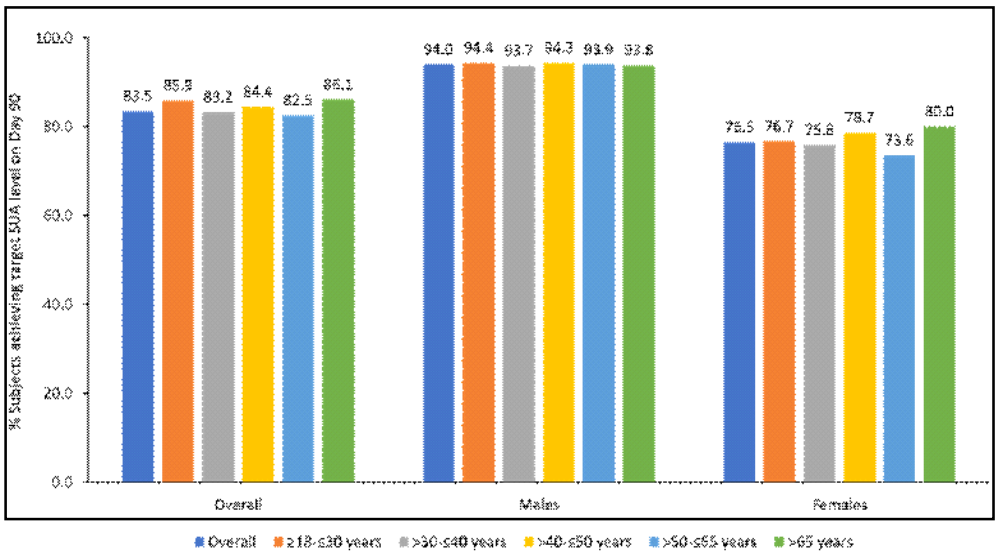

Fig 2 — Attainment of Target SUA Levels on Day 90 (PPpopulation)
PP = per protocol; SUA = serum uric acid

often not achieved[20]. Although the use of ULT is necessary for lowering and maintaining SUA levels within the target thresholds, little is known about how patients with elevated SUA levels manage their ULT[27].

Despite limited studies from India about adherence to ULT and the impact of intervention, insights are available from other parts of the world. Prospectively followed-up patients show high adherence rates and close to 90% of patients reach the SUA therapeutic target of <6.0 mg/dL[38]. In a site-randomized trial comparing a 1-year pharmacist-led intervention via automated telephone technology versus usual care for patients with gout initiating allopurinol, patients who underwent intervention were more likely to be adherent (50% *versus* 37%) and reach SUA goals (30% *versus* 15%) as compared to patients receiving usual care[29]. In another 1-year, single-center study employing intensive intervention administered by a specialty nurse and rheumatologist and including patient education with an individualized gout management plan, out of 106 patients with gout who were administered ULT, 96 (91%) completed the 1-year follow-up with the vast majority (92%) achieving the urate goal[30].

Regular monitoring can help in improving patient outcomes by keeping the SUA levels within the desired range. The results of this retrospective analysis suggest that the patient support initiative undertaken to aid patients and clinicians in SUA level monitoring was effective in improving ULT adherence and lowering elevated mean SUA levels in both male and female subjects and across all age groups. Of note, decline in SUA levels was lower among female subjects as compared with male subjects probably because of lower baseline levels. Regular monitoring had its impact on overall compliance to ULT, with 74.6% of patients continuing to be on ULT at the end of 90days. and 83.9% of patients achieving target SUA levels. Of note, despite the baseline mean SUA levels being ≥8.2 mg/dL in subjects aged ≤30 years, via high adherence rates during the monitoring period, a large proportion of these subjects could achieve SUA target levels by end of the study. It can be hypothesized that patients with higher baseline SUA levels (ie, poor hyperuricemic control) may be more attentive toward adherence to prescribed therapy.

To the best of our knowledge, this is the first Indian study, evaluating the impact of clinician-led regular monitoring on adherence to ULT and follow-ups in the Indian population. This retrospective analysis has attempted to present the effect of facilitating treatment compliance, regular monitoring, and patient education on SUA levels in Indian subjects on ULT. The collation of SUA level data for each patient on a real-time basis may have helped clinicians understand the level of SUA control needed over a period of time and the choice and dose of ULT to achieve therapeutic goals. Thus, the results of this retrospective data analysis present a well-defined effect of clinician-led intervention on SUA control.

However, our study has certain limitations that need to be acknowledged. Retrospective design and sample size not statistically powered can limit the inference-drawing ability of this study. Additionally, due to retrospective design, the scope of finding the association between the SUA levels and different patient characteristics was limited. However, we have analyzed data using standard definitions of conditions and outcomes. Moreover, we feel the results of this retrospective analysis will be useful in providing preliminary data to guide the design of future prospective studies.

Conclusions

In conclusion, results of this large, retrospective, multicenter study in Indian subjects support the need for regular monitoring of SUA levels to identify patients at risk of hyperuricemia and facilitate clinician-guided intervention to ensure adherence to ULT and achievement of SUA goals.

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