Raising Urate with Inosine to Potentially Slow Progression of Parkinson’s Disease

Results of the Phase II SURE-PD study show inosine is safe and tolerable and raises urate levels, which have been inversely related to Parkinson’s progression. Still, patients are cautioned against self-medicating before the next phase of this research effort is completed.

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Along the elusive road to neuroprotection for patients with Parkinson’s disease (PD), an important advance has been accomplished through carefully orchestrated elevations of urate levels in serum and spinal fluid. The Safety of Urate Elevation in Parkinson’s Disease (SURE-PD) trial was born from the converging evidence of an inverse association between urate levels and both the risk and the progression of PD. The risk of PD has been consistently shown to be lower\(^1\) and the speed of disease progression slower\(^2,3\) in a dose-dependent fashion with higher urate levels. Hence, urate had emerged as the first molecular predictor of both risk and progression of idiopathic PD.

A ROLE FOR URATE

Urate is a potent endogenous antioxidant and metal chelator and the end product of purine metabolism in humans. Remarkably, not only are urate levels lower among healthy people who are more likely to develop PD, but they are also lower among those already diagnosed with PD who tend to progress at a faster rate.\(^4\) There is epidemiologic, genetic, and basic science support in favor of such a neuroprotective effect of urate.\(^5\) Among some 1,600 early, untreated PD patients enrolled in the DATATOP and PRECEPT trials, those with baseline serum urate levels in the highest quintile (upper normal range) exhibited a 40 percent lower risk of clinical progression over two years compared to those with urate at or below the median of 6mg/dL.\(^2,3\) These outcomes were adjusted for age, smoking, caffeine intake, and other potential confounders. Similarly, in a subset of patients who underwent serial SPECT brain scans for changes in dopamine transporter (DAT) binding, patients with baseline urate levels in the highest quintile displayed a 70 percent slower rate of radiographic progression, as measured by loss of striatal DAT, compared to those with urate at or below the median.\(^2\)

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for the development of gout and uric acid kidney stones. The window between its toxic and potentially beneficial effects may be relatively narrow, suggesting that safety should be the initial focus of studies investigating elevating urate levels into a putatively protective range for PD. The SURE-PD Phase II trial was the concerted response to meet the needs of assessing safety, tolerability, and feasibility of long-term urate elevation in PD, an effort carried out by 17 Parkinson Study Group clinical sites in the US. From among the available pharmacological approaches to elevating urate, inosine offered the most practical strategy to elevating serum urate. Inosine is an orally bioavailable precursor of urate, widely consumed as a nutritional supplement, and previously administered in several multiyear clinical trials for multiple sclerosis.

**SURE-PD FINDINGS**

The results of the SURE-PD trial demonstrated that inosine is capable of raising serum and CSF urate in patients with early PD with reassuring safety data and excellent tolerability. SURE-PD was designed as a randomized, double-blind, placebo-controlled, dose-ranging trial of inosine and enrolled 75 early, largely untreated PD patients (mean age, 62 years; 55 percent women) with a baseline serum urate concentration less than 6mg/dL, the population median. Patients were randomized to one of three treatment arms: placebo, inosine aimed at raising urate mildly (6.1-7.0mg/dL), or inosine aimed at raising urate moderately (7.1-8.0 mg/dL). Inosine was administered in 500mg oral capsules, taken up to two capsules three times per day. Patients were followed for 24 months of intervention and after a one-month washout. The study was designed to assess safety, defined as the absence of unacceptable serious adverse events; tolerability, defined as continued treatment without adverse events requiring dose reduction; and the measurability of urate elevations in serum serially and in cerebrospinal fluid once at three months.

Inosine titrated to an average dose of 1.18 or 1.51g/d for up to two years was found to be generally safe, tolerable, and effective in raising serum and cerebrospinal fluid urate levels. Infrequent cardiovascular events occurred at the same or lower rates in the inosine groups relative to placebo. No participant developed gout and three receiving inosine developed symptomatic urolithiasis. Only one of these had a documented uric acid stone. This patient had tested positive for uric acid crystalluria and had a relatively low urine pH (5.5, just above the protocol-mandated trigger for prophylactic alkalinization). Treatment was tolerated by 95 percent of participants at six months, and no one withdrew because of an adverse event. Serum urate rose by 2.3 and 3.0mg/dL in the two dosing regimens, respectively, and such increases were documented as early as the first follow up visit, two weeks after treatment initiation. CSF urate levels were 40 percent and 50 percent higher in the inosine groups relative to placebo. Secondary analyses demonstrated nonfutility of inosine treatment for slowing disability, suggesting that a Phase III study assessing efficacy of inosine as disease modifier was warranted.

The results also are informative of several safety changes to be implemented in the design of the definitive Phase III clinical trial. These include collection of trough serum specimens to measure urate levels, and fewer titration visits to reach the urate target. Further, because urine pH was unaffected by inosine and the need for alkalinization was rare, home urinary pH measurement will be unnecessary. Quarterly urine sediment analysis for uric acid crystalluria may be more effective at predicting risk for urolithiasis. Sample size requirements for the Phase III study will be lower, given the absence of symptomatic effects of urate elevation when using change in the total Unified Parkinson Disease Rating Scale score as a primary endpoint.

**MORE STUDY NEEDED**

As the full safety profile of inosine requires further evaluation against its potential efficacy as a neuroprotectant in a Phase III study, patients are urged to refrain from unsupervised use of this drug. Serious side effects including gout, kidney stones and high blood pressure are still plausible complications if inosine elevates urate beyond a “therapeutic” range, particularly in the setting of preexistent risk factors, such as history of urolithiasis or prior myocardial infarction.

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