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Clinical Trial Design and Endpoints For Drugs Intended to Treat Gout

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Briefing Document

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Table of Contents

1.0 BACKGROUND

The underlying metabolic disorder in gout is hyperuricemia,[1] which is best defined physicochemically as an elevation in serum uric acid (sUA) to >7.0 mg/dL. This value just exceeds the limit of solubility of urate in extracellular fluids (6.8 mg/dL).[2] As serum uric acid values increase beyond about 7.0 mg/dL, extracellular fluids become supersaturated with urate, and the risk for crystal deposition and its consequences increase. Consequently, increasing incidence of gouty arthritis and uric acid urolithiasis parallels increasing levels of hyperuricemia. Hyperuricemia may result from increased uric acid production from either endogenous or exogenous sources, from decreased uric acid excretion due to deficits in renal urate handling, or from a combination of these two mechanisms. The majority of patients with hyperuricemia have a relative impairment in renal uric acid clearance.[3] Untreated gout can lead to painful, destructive arthropathy and urolithiasis can lead to renal failure.[3]

The incidence of gout ranges from 0.20 to 0.35 per thousand in various populations with an overall prevalence of 1.6 to 13.6 per thousand.[1] The incidence of gout directly increases with increasing serum uric acid levels. At serum uric acid levels between 7.0 and 8.9 mg/dl, the annual incidence rate of gout is 0.5%, for urate levels greater than 9.0 mg/dl, the incidence is 4.9% with a cumulative index of 22% after 5 years. In 9.2% of men with gout there is major limitation in physical activity.[1]

Tophaceous deposits occurred in approximately 50% of patients with gout prior to the availability of antihyperuricemic agents.[1] Treatment of tophaceous gout by reducing serum uric acid caused effective reduction and controlled the recurrence of tophi.[4-6] In a 10-year study of patients who were treated with antihyperuricemic agents, a clinical correlation between serum uric acid concentration and clinical tophaceous gout was noted.[7] Therefore, reduction in serum uric acid is key in controlling tophaceous gout.

Gout flares can be the result of dietary increases in purines, alcohol, stress or the result of the mechanism of action of antihyperuricemic agents.[1] Paradoxically, flares occur more frequently during the first few months of treatment with an antihyperuricemic agent,

possibly due to urate mobilization resulting in a rapid flux of urate levels. The initiation of treatment with the xanthine oxidase (XO) inhibitor, allopurinol, is commonly associated with acute gout flares. The incidence of gout flares in one study was 40% in the first month and 27% within the second month following the initiation of an antihyperuricemic agent, with fewer attacks noted during the following 3 to 6 months (6-11%). [8] Prophylactic treatments with colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) are recommended when treatment with allopurinol is initiated.[2,4] The decrease of prostaglandins and other inflammatory mediators by NSAIDs prevent the acute inflammation associated with gout flares while xanthine oxidase inhibitors, due to their mechanism of action, do not provide clinically significant anti-inflammatory activity.

2.0 CURRENT TREATMENT

Urate-lowering therapy is key in the management of patients with gout, frequent attacks of gouty arthritis, chronic gouty arthropathy, chronic tophaceous gout, renal impairment, or uric acid urolithiasis.[2, 9-16] The choice of urate-lowering agents includes uricosuric drugs, which enhance renal uric acid excretion, and the XOD inhibitor allopurinol, which reduces uric acid production.[2, 4,9,16]

The use of uricosuric agents has diminished since the introduction of allopurinol in the 1960's. [2,4,10,16] This is due, in part, to uricosuric agents having limited efficacy and/or safety in individuals with renal insufficiency or prior urolithiasis.[17] Also, one of the most potent uricosuric agents, benzbromarone, is unavailable in the United States (U.S.). [18] Allopurinol is an effective hypouricemic agent, but in the elderly, patients with impaired renal function or in transplant recipients, achieving a normal serum uric acid may be difficult.[4, 9, 11,16] Allopurinol use may also be limited by the uncommon, but potentially life-threatening allopurinol hypersensitivity syndrome, which is more common in elderly individuals and those with renal impairment. Reactions to allopurinol may also include: rashes, some severe; hematologic cytopenias; hepatitis; and vasculitis.[2, 4,16, 19-24]

3.0 PROPOSED TRIAL DESIGN FOR CHRONIC GOUT TREATMENT

The following trial design would be key in evaluating agents intended for the treatment or management of chronic gout.

1. Randomized, controlled, double-blind trial design.
2. Study population should include subjects with renal impairment and other comorbidities.
3. A proportion of subjects should include baseline serum uric acid values above 10 mg/dl.
4. Inclusion of placebo arm.
5. Inclusion of an active comparator arm.
6. Inclusion of a safety dose of the agent being evaluated (e.g., two times the anticipated maximum therapeutic dose).
7. At least one controlled study with a treatment duration of at least one year.
8. Inclusion of Health Related Quality of Life Outcome Measure.

4.0 PROPOSED ENDPOINT EVALUATION FOR CHRONIC GOUT TREATMENT

1. **Primary endpoint – Proportion of subjects who maintain a reduction of serum uric acid of <6.0 mg/dL, i.e., as measured by the last three laboratory values.**

Rationale

The primary treatment goal for the clinical manifestations of gout is the correction of hyperuricemia. A serum uric acid level of <6.0 mg/dL has been well established as the goal for gout treatment.[2-4, 6] A prospective study of 57 patients with a history of gout who were followed for over 10 years showed that those with a serum uric acid of ≤6.0 mg/dL had less urate crystals in synovial fluid, had reduction in tophi size and had a lower frequency of gout attacks over time.[13] In a retrospective analysis of 350 patients with gout, the optimal range of serum uric acid, which minimizes the risk of gouty arthritis was confirmed as <6.0 mg/dL.[8]

Hyperuricemia is also a cause for secondary gout caused by tumor lysis syndrome. Recently, the recombinant form of urate oxidase (Rasburicase®) was approved using serum uric acid as the primary endpoint for the treatment of hyperuricemia associated with tumor lysis syndrome.[26]

Measurement

Measurement of serum uric acid over the course of treatment with an antihyperuricemic agent.

2. **Clinical endpoint - reduction of tophi size and/or number.**

Rationale

A prospective study of 63 patients with tophaceous gout revealed that a reduction in tophi occurred when serum uric acid was <6.0 mg/dL.[7] This study further demonstrated that tophi resolved faster when a lower mean concentration of serum uric acid was achieved (sUA 3.97 ± 0.76 mg/dL with a tophi reduction rate of 1.53 ± 0.45 mm/month compared to sUA 5.37 ± 0.79 mg/dL and tophi reduction rate of 0.57 ± 0.18 mm/month). In a study of 39 patients with gout followed over 10 years who were treated with antihyperuricemic agents, patients who had a reduction in tophi size had a mean serum uric acid of 6.2 mg/dL.[14] Those who had no reduction or an increase in tophi size had a mean serum uric acid of 8.2 mg/dL.

Measurement

Measurements of tophi may be made by a simple physical measurement of the nodules.[27] In addition, radiographic techniques such as Magnetic Resonance Imaging (MRI) and ultrasound may be useful in following the progression of tophaceous deposits.[28, 29] However, these radiographic techniques may be limited by location and size of tophus.

3. **Clinical endpoint - reduction of long-term gout flares.**

Rationale

Serum uric acid levels must be maintained at <6.0mg/dL to prevent the recurrence of tophi and acute gout attacks.[5,6] Noncompliance with treatment has also been shown to contribute to worsening disease. A study of 60 gout patients revealed that 22 (37%) noncompliant patients had higher serum uric acid (>9.0 mg/dL) than those who were compliant.[30] These patients had clinically and radiographically evident tophaceous gout and frequent polyarticular gouty attacks. Another study of 106 gout patients revealed that

22 (21%) had tophaceous gout associated with noncompliance, increased duration of hyperuricemia and oligoarticular or polyarticular gouty arthritis.[31]

Measurement

Chronic gout flares may be measured by evaluating the frequency of flares over time after an initial period of 3 to 6 months. The proportion of subjects that required treatment intervention to manage gout flares, eg, NSAIDs, steroid or colchicine, may characterize these chronic flares.

5.0 PROPOSED HEALTH RELATED QUALITY OF LIFE EVALUATION FOR CHRONIC GOUT TREAMENT

Background

Patient reported outcomes are an important source of information to clinical decision makers.[32] These outcomes include but are not limited to health related quality of life (HRQOL), functional status, satisfaction with treatment, work productivity, and disability. The use of HRQOL and other patient reported outcome measures to capture appropriate data offers a way to monitor disease effects and treatment impacts in terms that are relevant to patients and that reflect the quality of their lives in general as well as on specific aspects of their lives such as work. Patient global health status assessment and functional status have been internationally recommended as core outcomes to be measured in clinical trials in RA.[33]

While gout has been diagnosed for centuries, the humanistic burden of gout appears to be relatively unexplored. This is not too surprising given that the last new treatment for gout was introduced before there was significant interest in health outcomes research and the development of patient reported outcomes assessment.

However with renewed interest in gout treatments, and the knowledge that gout is expected to be frequently encountered as the prevalence of obesity and type 2 diabetes mellitus continue to rise in the U.S., [34] consideration of patient reported outcomes in gout clinical trials is a timely topic for discussion.

Rationale

Given the lack of information in the literature, guidance regarding what types of patient reported outcomes to include in gout trials needs to come from other sources and should be considered work in progress. Given that gout is a chronic disease, with symptoms of pain, swelling, and tophi, it is reasonable to consider aspects of functioning, well being, symptom relief and satisfaction as types of patient reported outcomes that may be of interest in clinical trials.

Measurement

It has previously been recommended that general and disease-specific quality of life measures be used in clinical trials of chronic conditions, [35] and initially that would appear to make sense in gout patients as well. The general HRQOL assessment allows comparisons of conditions beyond gout, but also may demonstrate the condition or a treatment that may have an impact on the patient that was not expected (in a domain that was not hypothesized).

The SF-36 is a 36-item general HRQOL measure with established psychometric properties.[36] It measures 8 general health concepts and health transition. Each concept is scored separately, but they are also summarized as physical and mental component scores. The SF-36 is reliable and valid in general and ambulatory populations and in populations with chronic diseases.[37] Its use has been reported in longitudinal as well as randomized controlled trials in patients with active rheumatoid arthritis[38, 39] and osteoarthritis.[40] We would recommend that the SF-36 be the general instrument considered for use in gout trials.

A literature search identified no gout-specific patient reported outcome instruments; therefore TAP developed such an instrument, the Gout Assessment Questionnaire (GAQ). This 21-item questionnaire covers 7 domains and has been included in clinical trials evaluating the safety and efficacy of a gout treatment.

Initiation of therapy with a serum uric acid lowering agent may result in more acute gout flares, consequently improvement in patient reported outcomes may not be noted until after at least 6 months of treatment when the serum uric acid has a chance to stabilize. In addition, it may take up to 1 year for total body urate load to decrease to a normal level, especially in subjects with tophaceous deposits and high serum uric acid. Therefore, it is reasonable to evaluate longer-term data (12 months or greater) when considering the impact of gout treatment from the patient's perspective.

6.0 CONCLUSION

The literature supports the reduction of serum uric acid to <6.0 mg/dL as providing a clinical benefit in terms of the manifestations of gout. There is strong evidence of a correlation between reducing serum uric acid, tophi reduction and decreasing frequency of gout flares over time. Health related quality of life measures of functioning, well being, symptom relief and satisfaction as types of patient reported outcomes should also be considered in clinical trials.

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