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Gouty Arthritis: A Novel Therapeutic Approach for Highly Resistant Patients.

Stephen Soloway[1], Alyxandra Soloway[2], Tyler G. Chin[3], Joseph Colombo[4]

[1]Inspira Heath Network Chairman Of Rheumatology,Department of Internnal Medicine, Aland Islands

[2] Inspira Health Network- Rheumatology, Aland Islands

[3] Ursinius College ; Biology/Medicine, Aland Islands

[4] Stephen Soloway , MD, Rheumatology, Aland Islands

Corresponding Author: Joe Colombo PhD; Rheumatology, 2848 S. Delsea Dr., Suite 2C, Vineland, NJ, USA 08360; P: 856-794-9090; F: 856-794-3058; email: dovetech@erols.com

ABSTRACT

Introduction. Gouty arthritis normally is well controlled. Under extreme circumstances patients for various reasons may have to use Pegloticase (Krystexxa). About 30% of patients on Krystexxa develop immunogenicity or tolerance to the medication rendering it useless, and with use of immunosuppressants this tolerance can be blunted in almost 50% of patients, which leaves 15% with dialysis. To our knowledge, the first cases of severe gout and intolerance of Krystexxa, who were then placed on Allopurinol (Zyloprim) and Febuxostat (Uloric) and received a considerable benefit are presented in this clinical study. **Methods**. Three patients were diagnosed with Gouty arthritis and found intolerant of Krystexxa. Allopurinol 600mg daily with a taper of corticosteroids, history dependent, were introduced.

Patients found to have uric acid levels that remained high were prescribed Uloric 40mg, titrated to 80mg as needed. **Results**. All patients' uric acid levels were reduced from >12mg/dL to < 4 mg/dL and maintained at the lower levels. **Conclusion**. In cases of severe gout and intolerance of Krystexxa, Allopurinol and Uloric may provide considerable benefit.

Keywords: Gout, Arthritis, Polymyalgia Rheumatica, Psoriatic Arthritis, Pegloticase (Krystexxa), Allopurinol (Zyloprim), Febuxostat (Uloric).

INTRODUCTION

Gout is one of the most common inflammatory arthritis in the United States occurring in 5% of the population [1]. Gouty arthritis is associated with significant morbidity and mortality and is caused by hyperuricemia. Gout is effectively managed and potentially cured by decreasing the overall urate burden with serum urate-lowering therapy. [2]. Gouty arthritis normally is well controlled. Under extreme circumstances patients for various reasons may have to use Pegloticase (Krystexxa). About 30% of patients on Krystexxa develop immunogenicity or tolerance to the medication rendering it useless [3,4], and with use of immunosuppressants, medications such as Methotrexate, this tolerance can be blunted in almost 50% of patients [5,6], which leaves 15% of refractory gout patients with dialysis.

To our knowledge, the first three cases of severe gout and intolerance of Krystexxa, who were then placed on Allopurinol (Zyloprim) and Febuxostat (Uloric) and received a considerable benefit are presented in this clinical study.

METHODS

Three patients (100% male; averages: age, 53y/o. height, 5'10", weight, 295#) with crystal proven Gout. All patients UA levels were > 12mg/dL at first presentation (average UA = 14.7mg/dL) with non-healing tophus and severe erosion, patients were treated with Krystexxa, one dose per two weeks. Krystexxa, a uric acid specific enzyme, that is a recombinant uricase (urate-oxidacs) and achieves its therapeutic effect by catalyzing the oxidation of UA to Allantoin (a major metabolic intermediate), thereby lowering serum UA. Upon Krystexxa intolerance, patients were switched to Allopurinol 600mg daily with corticosteroids in a

tapering dose over 6 weeks. Patients found to have uric acid levels that remained > 6.6mg/dL were prescribed Febuxostat (Uloric) 40mg, titrated to 80mg as needed. The average duration of gout was 10 to 12 years.

RESULTS

Patient 1 is a 58y/o white male, 6'1", 290#, with severe polyarticular gout, tophus coming through the skin of his chest wall and most peripheral joints, with history of hypertension and diabetes, history of deep vein thrombosis, pulmonary embolism and osteoma, and prescribed Zoledronic acid, Diltiazem, Hydralazine, and Warfarin. The patient denied smoking and alcohol. The patient's UA was 15.6mg/dL on initial presentation. For the first six treatments of Krystexxa the patient's UA was 0mg/dL. During that period of time he was feeling better and his gout started to clear up with less visible tophus. After intolerance to Krystexxa, Alopurinol daily with corticosteroids helped to reduce the patient's UA to 6.5 to 6.8mg/dL. Uloric 40mg daily was added and reduced UA to 5.8 to 6.2mg/dL. Uloric was titrated to 80mg daily and to current the patient's UA remains between 3.5 and 4.0mg/dL. Over the past two years there were no gout attacks reduced tophus burden, (tophi in both elbows olecranon and left third distal interphalangeal joints, right third and fourth proximal interphalangeal joints, which have shrunk, remain). The patient has maintained, from inception (2017) until current (2022), normal white count (6.2cmm), hemoglobin (14.1g/dL), and platelets (306,000/mcl), Hyperglycemia (120 to 150mg/dL), serum creatinine (1.0mg/dL), glomerular filtration rate (86mL/min), serum glutamic-oxaloacetic transaminase (40units/L) and serum glutamic pyruvic transaminase (44units/L), uric acid (3.4mg/dL), and Urinalysis with no protein, no blood.

Patient 2 is a 68y/o black male, 5'8", 300#, with history of hypertension, diabetes, mild chronic renal insufficiency, with baseline uric acid of 16mg/dL, severe tophaceous gout extruding from hands, fingers, with lysis of multiple joints, resulting in disability. The patient's chemistry, CBC, hemoglobin, platelets, liver function, renal function, and urinalysis were normal. Two injections of Krystexxa brought his UA to 0mg/dL. After one-month UA was 8.0mg/dL. With Alopurinol and Prednisone (tapered over two months), his pains, mostly polyarticular have subsided markedly, likely from the corticosteroids; however, UA remained >6mg/dL and Uloric was titrated from 40 to 80mg. Since 2018 the patient's UA has

been maintained between 3 and 4mg/dL, disease free off corticosteroids, with no gout attack or renal stone disease.

Patient 3 is a 45y/o white male with history of hypertension, cardiovascular disease, with an MI (subendocardial); prescribed Ramipril, Atorvastatin, baby aspirin, and 12.5mg Coreg; serum UA between 12 and 13mg/dL, with normal chemistry, complete blood count, liver functions, with continuous attacks of monoarthritis in the first right metatarsophalangeal joint and the left knee, with more than five attacks of gout with intracellular urate crystals. X-rays taken one year after first presentation showed rapid progression of erosions in the first and second right metatarsophalangeal joints. Fluid from those joints revealed negative cultures and intracellular monosodium urate. Krystexxa reduced the UA to 0mg/dL for approximately 8 months until intolerance. Allopurinol with a two-month taper of steroids stopped gout attacks, but UA remained >6.2mg/dL. Uloric titration from 40 to 80mg reduced UA to 3 to 3.5mg/dL.

With Allopurinol 600mg daily and Uloric 80mg, all patients' UA was maintained ≤ 4.0mg/dL relieving the gout.

CONCLUSION

Most gout patients are generally managed without biologic therapy such as Krystexxa. Patients who require Krystexxa particularly in light of combination with Methotrexate have a 15% chance of tolerating the drug [3,5]. Although only three patients are reported; there are three patients who are safely maintained on high but not maximal dose of Alopurinol in combination with high but not maximal dose of Uloric. These patients all maintained UA between 3 to 4mg/dL, safely, regardless of diet or alcohol consumption, including a 12 pack of beer several times/week (Patient 2) and 1.75L/day whiskey (Patient 3). My speculation is that since (1) purine inhibition and pyrimidine inhibition, Alopurinol and Uloric respectively, can be safely combined when necessary for the unique group of patients that have a severe enough need for Krystexxa, and (2) should Krystexxa be unavailable due to cost or other reason or not feasible due to tolerance, (3) the combination of Alopurinol and Uloric is a safe and effective approach in treating severe tophaceous gout.

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Data Availability Statement: All data are HIPAA protected and available upon request.

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