PRETREATMENT AND CO-ADMINISTRATION WITH METHOTREXATE IMPROVED DURABILITY OF PEGLOTICASE RESPONSE: A PROSPECTIVE OBSERVATIONAL, PROOF-OF CONCEPT, CASE SERIES

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Background

- Pegloticase is a recombinant DNA-produced porcine-like uricase enzyme, which metabolizes relatively insoluble urate to highly soluble allantoin. It is used in the treatment of refractory gout which has failed maximal medical management, typically with xanthine oxidase inhibitors (XOI).
- Studies have shown a complete responder rate of 42% when defined as repeat serum uric acid (sUA) levels <6.0 mg/dL for >80% of the time during months 3 and 6 of treatment.
- Patients that do not maintain a low uric acid while on pegloticase therapy are presumed to have developed anti-drug antibodies (ADA) which rapidly clear the pegloticase molecule.
- As is routinely utilized in the treatment of other rheumatologic diseases, coadministration of immunomodulatory medications, such as methotrexate, could potentially temper the development of these ADAs (as defined by maintenance of sUA response) in patients treated with pegloticase for refractory gouty arthropathy.
- The aim of the current case series was to identify and clinically evaluate patients in a real-world practice setting in order to investigate the utility of adding methotrexate to a pegloticase regimen to increase the durability of response.

Methods

- In this prospective, proof-of-concept, observational case series, 10 sequential patients with refractory tophaceous gouty arthropathy being started on treatment with pegloticase 8 mg every two weeks (as per the label) were identified from 3 separate infusion centers.
- No inclusion/exclusion criteria were implemented or prescreening performed.
- Methotrexate (MTX) 15 mg orally once weekly and folic acid 1 mg orally once daily was started one month prior to the initial administration of pegloticase and continued throughout pegloticase treatment.
- Any infusion pre-medications, which were consistent with standard practices, were administered per the individual physician's discretion as well as management of any gout flares, which occurred during the treatment course.
- As per standard of care, sUA was measured every two weeks, prior to each subsequent infusion.
- At the completion of pegloticase treatment for all patients, the number and percentage of patients able to maintain an sUA at goal <6.0 mg/dL was recorded.

Results

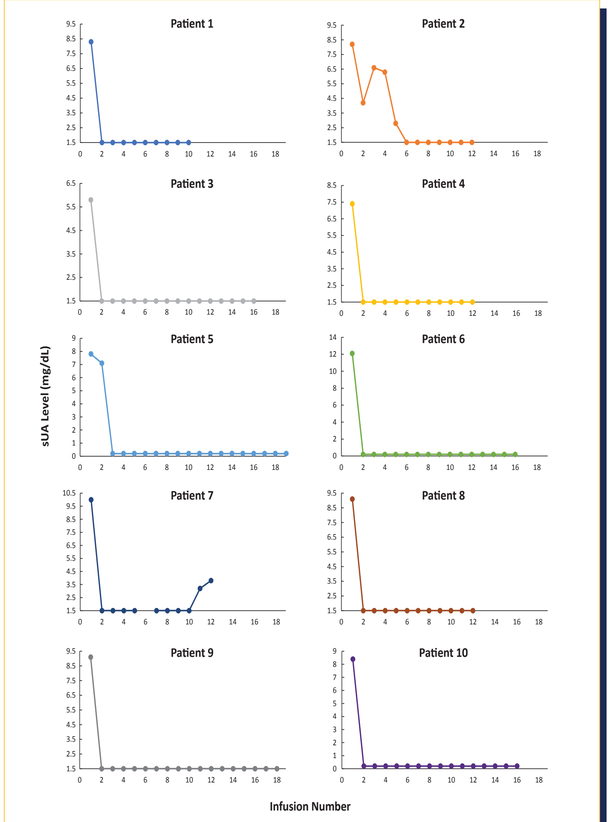
- Ten patients ranging in age from 35-80 were identified, from 3 separate infusion centers (**Table 1**).

Table 1. Patient Baseline Characteristics

Patient	Sex	Age	Comorbidities	Previous Gout Treatment	Year of Gout Diagnosis	Baseline sUA
1	M	45	Epilepsy, Depression, Anxiety, Insomnia, Sleep Apnea	Allopurinol 600 mg QD & Febuxostat	1991	8.3 mg/dL
2	M	50	None	Allopurinol	Unknown	8.2 mg/dL
3	M	41	Renal Insufficiency	Allopurinol & High Dose Febuxostat	1997	5.8 mg/dL
4	F	80	Psoriatic Arthritis, Senile Osteoporosis, Renal Failure, Hypertension, Cholesterol, Heart Block with Pacemaker, Valvular Heart Disease, Parathyroid Tumor	Febuxostat 80 mg	Unknown	7.4 mg/dL
5	F	67	Hyperlipidemia, Neoplasm Right Foot, Palpitations	None	2017	7.8 mg/dL
6	M	35	Insomnia	None	>10 years	12.1 mg/dL
7	M	50	Hypertension, Type 2 Diabetes Mellitus	Allopurinol	1993	10.0 mg/dL
8	M	51	None	Allopurinol	2003	9.1 mg/dL
9	M	44	Type 2 Diabetes Mellitus, Depression, Anxiety, Osteoarthritis, Hypertension, Asthma	Allopurinol	1995	9.1 mg/dL
10	M	55	Hypertension, Hyperlipidemia, Non-traumatic Subarachnoid Hemorrhage, Osteoarthritis Cervical Spine	None	Unknown	8.4 mg/dL

- There were 143 total pegloticase infusions performed within the observation period.
- All 10 patients received at least 10 infusions (5 months), 9 patients at least 12 infusions (6 months), 5 patients at least 16 infusions (8 months), and 3 patients at least 18 infusions (9 months).
- All patients stayed on MTX 15 mg/week. No methotrexate dose adjustments were needed.
- All 10 patients completed a full course of pegloticase treatment.
- 100% of patients were responders as defined by >80% of sUA levels being maintained at goal <6.0 mg/dL during the observation period (**Figure 1** and **2**).

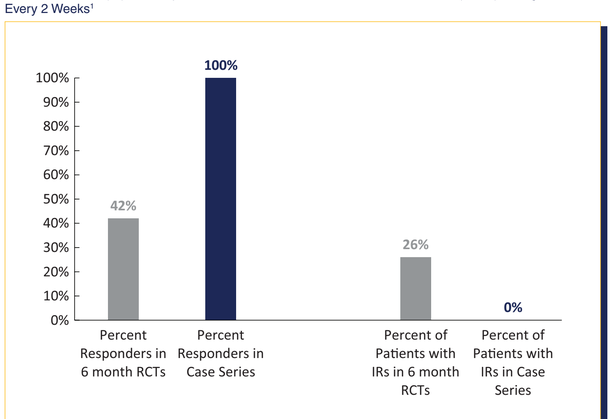
Figure 1. Pre-Infusion Serum Uric Acid of Each Patient Over Time



Note: Y-axis minimum set to lower limit of detection for assay (1.5 or 0.2 mg/dL).

- None of the 10 patients stopped pegloticase therapy due to increased sUA or loss of response and there were no infusion reactions in any of the 143 infusions or safety concerns identified (**Figure 2**).

Figure 2. Percentage of Pegloticase (+ Methotrexate) Responders and Percentage of Patients with an Infusion Reaction (IR) as Compared with Results of Randomized Controlled Trials (RCTs) of Pegloticase Every 2 Weeks[1]



- DECT imaging was performed on one patient prior to pegloticase treatment, after 12 infusions, and after 18 infusions showing reductions in total tophi burden volume (**Figure 3**).

Figure 3. DECT Imaging of Patient 9

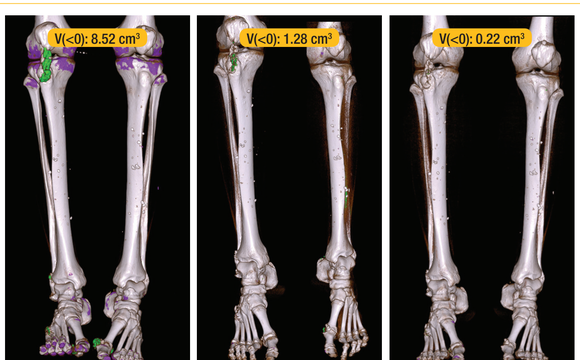
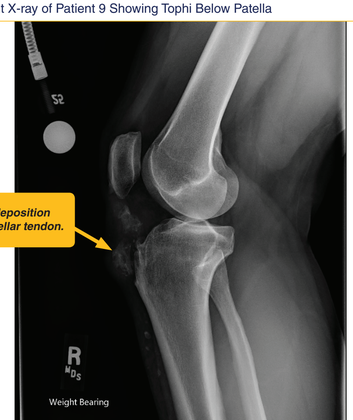


Figure 4. Pretreatment X-ray of Patient 9 Showing Tophi Below Patella



- Gout flares did occur primarily following the initial infusions, with less severity/prevalence with subsequent infusions.
- During therapy, 7 of 10 patients had at least one gout flare.
- No patient discontinued treatment because of flares.

Conclusions

- In this proof-of-concept case series of 10 sequential patients, pretreatment and co-administration of methotrexate 15 mg orally once weekly and folic acid 1 mg orally once daily with pegloticase resulted in a 100% maintenance of pegloticase sUA response with no infusion reactions.
- All 10 patients completed a full course of pegloticase treatment.
- Although additional studies would be needed to corroborate these results, these data support a potential paradigm shift in treatment of refractory gout with pegloticase.

Reference

1. Sundy JS, et al. *JAMA*. 2011;306:711

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