Febuxostat: From Gout Management to Neurosurgery and Beyond

J.Sales-Llopis

Neurosurgery Department, Alicante University General Hospital, Alicante, Spain.

Abstract

Febuxostat is a medication prescribed to lower uric acid levels in individuals with gout, a condition characterized by the accumulation of uric acid crystals in the joints. This abstract provides a concise overview of key aspects related to febuxostat, its indications, mechanism of action, and considerations for use. Additionally, it discusses the potential of febuxostat in the context of neurosurgery and the study's findings related to its effects on long noncoding RNAs (lncRNAs) after intracerebral hemorrhage. Furthermore, it touches on the CAALA regimen's development, emphasizing the combination of drugs to enhance the efficacy of 5-aminolevulinic acid (5-ALA) in glioblastoma treatment. Lastly, the abstract addresses concerns regarding the cardiovascular safety of febuxostat and allopurinol, highlighting data from the FDA Adverse Event Reporting System (FAERS) database.

These diverse topics underscore the potential of febuxostat in various medical contexts, from gout management to neurosurgery and glioblastoma treatment. However, they also underscore the importance of rigorous research, safety assessments, and individualized patient considerations when utilizing febuxostat and similar medications.

Keywords: Febuxostat, gout, uric acid, neurosurgery, glioblastoma, 5-aminolevulinic acid, cardiovascular safety, adverse events.

Introduction

Febuxostat is a medication used to lower uric acid levels in the body. It is primarily prescribed to individuals with gout, a type of arthritis caused by the accumulation of uric acid crystals in the joints. Here are key points about febuxostat:

Indication: Febuxostat is indicated for the treatment and management of hyperuricemia (elevated levels of uric acid) in patients with gout. It helps reduce the production of uric acid and can prevent the formation of uric acid crystals in the joints and kidneys.

Mechanism of Action: Febuxostat works by inhibiting the enzyme xanthine oxidase, which plays a crucial role in the conversion of purines into uric acid. By blocking this enzyme, febuxostat reduces the production of uric acid in the body.

Uric Acid Reduction: One of the primary goals of febuxostat is to lower the levels of uric acid in the blood. Lowering uric acid levels can help prevent gout attacks and alleviate the symptoms associated with gout.

Dosing: The appropriate dosage of febuxostat is determined by a healthcare provider based on the individual's condition and uric acid levels. It is typically administered orally in the form of tablets.

Maintenance Therapy: Febuxostat is often prescribed as a long-term or maintenance therapy for individuals with gout. Continuous use is necessary to manage the condition effectively and prevent gout attacks.

Side Effects: As with any medication, febuxostat can have side effects. Common side effects include gastrointestinal discomfort, skin rash, and liver function abnormalities. More severe side effects are rare but possible. Any unusual or severe side effects should be reported to a healthcare provider.

Drug Interactions: Febuxostat may interact with other medications, potentially affecting their effectiveness or increasing the risk of side effects. It is crucial to inform healthcare providers about all medications being taken when febuxostat is prescribed.

Monitoring: Regular monitoring of uric acid levels and liver function is typically recommended while taking febuxostat. This helps ensure that the medication is effectively managing uric acid and is not causing harm to the liver.

Diet and Lifestyle: In addition to medication, lifestyle and dietary changes, such as reducing the consumption of foods high in purines and maintaining a healthy weight, can also help manage gout and hyperuricemia (high uric acid levels).

Long-Term Use: Febuxostat is generally considered safe for long-term use when prescribed and monitored by a healthcare provider. It can significantly improve the quality of life for individuals with chronic gout or other conditions associated with high uric acid levels.

Overall, febuxostat is an effective medication for managing gout and conditions related to elevated uric acid levels. Its use should be under the supervision of a healthcare provider who can determine the appropriate dosage, monitor its effects, and assess any potential interactions with other medications.

Indications in neurosurgery

A study was conducted to investigate whether febuxostat protects brain via regulating long noncoding RNAs after ICH. The modified neurological severity score, wire hanging test, Evans blue perfusion and immunofluorescence were performed to test the protective effects of febuxostat in a mouse model of ICH. Whole transcriptome sequencing was conducted to identify the lncRNAs affected by febuxostat and their functions were analyzed. Febuxostat ameliorated behavioral abnormalities and protected the blood-brain barrier after ICH. Fifteen lncRNAs regulated by febuxostat after ICH were detected. These 15 lncRNAs were associated with 83 gene ontology items. In total, 35 genes, 15 mRNAs and 202 miRNAs were regarded as potential targets for the 15 lncRNAs; 183 co-expressed genes were identified for these 15 lncRNAs and the co-expression network was constructed. Potential binding between lncRNAs and mRNAs was also studied. Enrichment analysis revealed that the functions of the 15 lncRNAs were related to maintaining the blood-brain barrier. This study demonstrated febuxostat protected brain after ICH. Fifteen lncRNAs were regulated and were associated with the effects of febuxostat on BBB integrity after ICH [1)].

The findings should be viewed as preliminary, and further research is needed to validate and extend these results. The translational potential of febuxostat as a therapeutic option for ICH patients will require rigorous investigation in both preclinical and clinical settings.

The CAALA (Complex Augmentation of ALA) regimen was developed with the goal of redressing some of the weaknesses of 5-aminolevulinic acid (5-ALA) use in glioblastoma treatment as it now stands. 5-ALA is approved for use prior to glioblastoma surgery to better demarcate tumor from brain tissue. 5-ALA is also used in intraoperative photodynamic treatment of glioblastoma by virtue of uptake of 5-ALA and its preferential conversion to protoporphyrin IX in glioblastoma cells. Protoporphyrin IX becomes cytotoxic after exposure to 410 nm or 635 nm light. CAALA uses four currently-marketed drugs-the antibiotic ciprofloxacin, the iron chelator deferiprone, the antimetabolite 5-FU, and the xanthine oxidase inhibitor febuxostat-that all have evidence of ability to both increase 5-ALA mediated intraoperative glioblastoma demarcation and photodynamic cytotoxicity of in situ glioblastoma cells. Data from testing the full CAALA on living minipigs xenotransplanted with human glioblastoma cells will determine safety and potential for benefit in advancing CAALA to a clinical trial [2)]

While the idea is promising, it must be subjected to rigorous preclinical testing and, if found safe and effective, clinical trials to establish its practicality and benefits. Furthermore, careful consideration of the safety and ethical aspects of combining multiple drugs is essential. Only through well-executed research and validation can the potential of CAALA be fully assessed, and its clinical utility determined.

Complications

Febuxostat and allopurinol are the most commonly used uric acid-lowering medications, and their safety is of great concern, especially the cardiovascular adverse reactions associated with febuxostat. We propose to study the cardiovascular toxicity of febuxostat and allopurinol using the FDA Adverse Event Reporting System (FAERS) database.

A total of 64 quarters of FAERS data were downloaded from 2004 to 2019. Febuxostat- and allopurinol-related cardiovascular adverse events were extracted after data cleaning. Signal detection was conducted by reporting odds ratio (ROR) and proportional reporting ratio (PRR).

There were 2939 and 25,219 reports of febuxostat- and allopurinol-related cardiovascular adverse events (CVAEs), respectively. The most frequent CVAEs with febuxostat and allopurinol were edema peripheral (14.38%) and peripheral swelling (8.76%), respectively. In elderly gout patients, febuxostat is associated with an increased risk of heart failure, ischemic heart disease, hypertension, and cardiomyopathy. Febuxostat in combination with acetic acid derivatives nonsteroidal anti-inflammatory drug (NSAIDS) also increases the risk of cardiovascular adverse events.

Compared with allopurinol, febuxostat may increase cardiovascular toxicity in patients with gout [3)].

The review contributes to the understanding of the cardiovascular safety of uric acid-lowering

medications. It highlights the potential risks associated with febuxostat, especially in certain patient populations. However, it is crucial to recognize the limitations of the FAERS database, the need for further research to confirm these findings, and the importance of individualized risk-benefit assessments when prescribing these medications for gout management.

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