Joint Bone Spine 84 (2017) 541–546

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Review

Severe gout: Strategies and innovations for effective management

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ARTICLE INFO

Article history:
Accepted 10 October 2016
Available online 5 December 2016

Keywords:
Severe gout
Refractory
Management
Colchicine
Allopurinol
Febuxostat
Tophus

ABSTRACT

Severe gout is characterised by frequent polyarticular flares, numerous tophi, joint damage, and musculoskeletal disability. This is a preventable condition and in many cases, represents a disease that has been insufficiently managed for years. Standard management recommendations may be insufficient for patients with severe gout; these patients frequently require intensive individualised pharmacological management with combinations of urate-lowering therapy and anti-inflammatory agents. In this article, we aim to integrate recent therapeutic advances to provide a practical framework for optimal management of severe gout.

1. Introduction

In clinical practice, severe gout presents as frequent polyarticular flares, extensive tophaceous deposits, joint damage, and musculoskeletal disability. Although there is no widely accepted definition for severe gout, the recent American College of Rheumatology (ACR) Gout Management Guidelines have defined as severe chronic tophaceous gouty arthropathy those cases with ">4 tophi, or at least one unstable, complicated or severe tophus" [1]. In the clinical trials of pegloticase, for which a definition to select patients was necessary, gout was considered as 'refractory' if the following were present: "a baseline serum urate (SUA) ≥8.0 mg/dl and 3 or more self-reported gout flares in the previous 18 months, 1 or more tophi, or gouty arthropathy." [2]. A threshold of 5 tophi has also been used in other studies to define gout as severe [3]. None of these definitions is evidence based; since severity and its consequent management difficulties occur as a continuum and may be influenced by other circumstances, these definitions insufficiently cover those scenarios where management difficulties may occur. For this article, we consider severe gout to be characterised by a large burden of accumulated monosodium urate (MSU) crystals with associated joint damage (Fig. 1), and/or frequent or even continuous flaring, oligo or polyarticular flares, associated comorbidities (such as chronic kidney disease (CKD), heart failure or metabolic syndrome), and/or drug intolerance.

In the last decade, there have been major advances in the understanding and management of gout, with approval of new therapeutic agents, publication of treatment guidelines, and identification of therapeutic SUA targets for effective management of gout. In this article, we aim to integrate these advances to provide a practical framework for optimal management of severe gout. Key management points are summarised in Table 1 and a decision tree is shown in Fig. 2. Local drug availability and approvals should be considered by individual readers.

The key concept for effective management for all patients with gout is that this is a *reversible* crystal deposition disease, so the central aim of treatment is the reduction and final elimination of monosodium urate (MSU) crystals by normalising SUA levels [2,4–6]. Additionally, flares occurring during initiation or during of urate-lowering therapy should be avoided, and if flares do occur, they should be rapidly and effectively treated. Attention must be paid to comorbidities that may result from gout or complicate its management. Finally, patients must be informed of the characteristics of the disease, its treatment, and the role of the different drugs required. These five components of gout management may pose difficulties in those patients with severe disease, especially when the patient considered as a failure previous attempts of treatment [6].

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http://dx.doi.org/10.1016/j.jbspin.2016.10.004
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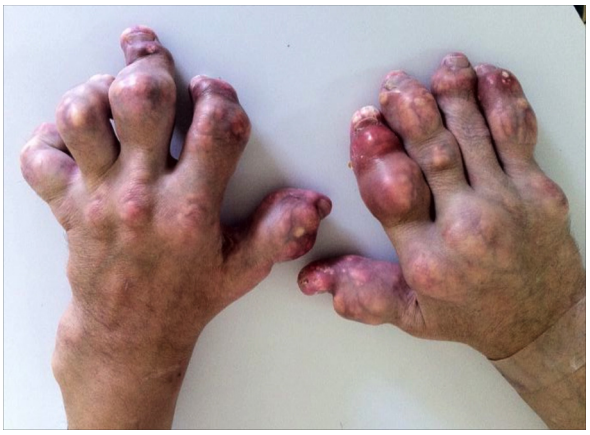

Fig. 1. Example of severe gout. Numerous large tophi with associated joint deformity in the hands of a young patient with severe gout.

Table 1
Key points in the management of severe gout.

Patients with severe gout often have insufficient response to standard management approaches and require intensive individualised pharmacological treatment
In patients with severe gout, serum urate levels well below 5 mg/dl (300 μmol/l) are required to enhance crystal dissolution, using urate-lowering drugs at maximal doses or in combination
Flexible prophylaxis is needed as flares often occur after serum urate reduction in patients with severe gout
Comorbidities such cardiovascular or kidney disease are common in patients with severe gout and often determine therapeutic approaches
Severe gout is often the result of neglected disease; effective urate-lowering therapy should be established in people with gout well before the development of extensive MSU crystal deposition, tophi, and joint damage

2. Reduction of SUA levels

In a prospective study of joint aspirations in patients with gout on urate-lowering therapy, the recommended therapeutic SUA target of <6 mg/dl [*to convert into μmol/l, multiply 59.48*] resulted in crystal dissolution in 16 out of 19 patients sampled [7]. Values below 5 mg/dl are now recommended for severe gout by the European League Against Rheumatism [5], the British Society for Rheumatology [8] and the ACR [1]. Lower SUA values lead to faster diminution of tophus size and earlier disappearance: SUA values <4 mg/dl result in twice the rate of tophus diameter reduction than values >5 mg/dl [9]. Profound SUA lowering by pegloticase also results in fast disappearance of tophi [2]. By setting the SUA target we are deciding on the time to crystal disappearance. When the burden of accumulated MSU crystals is very large, SUA targets

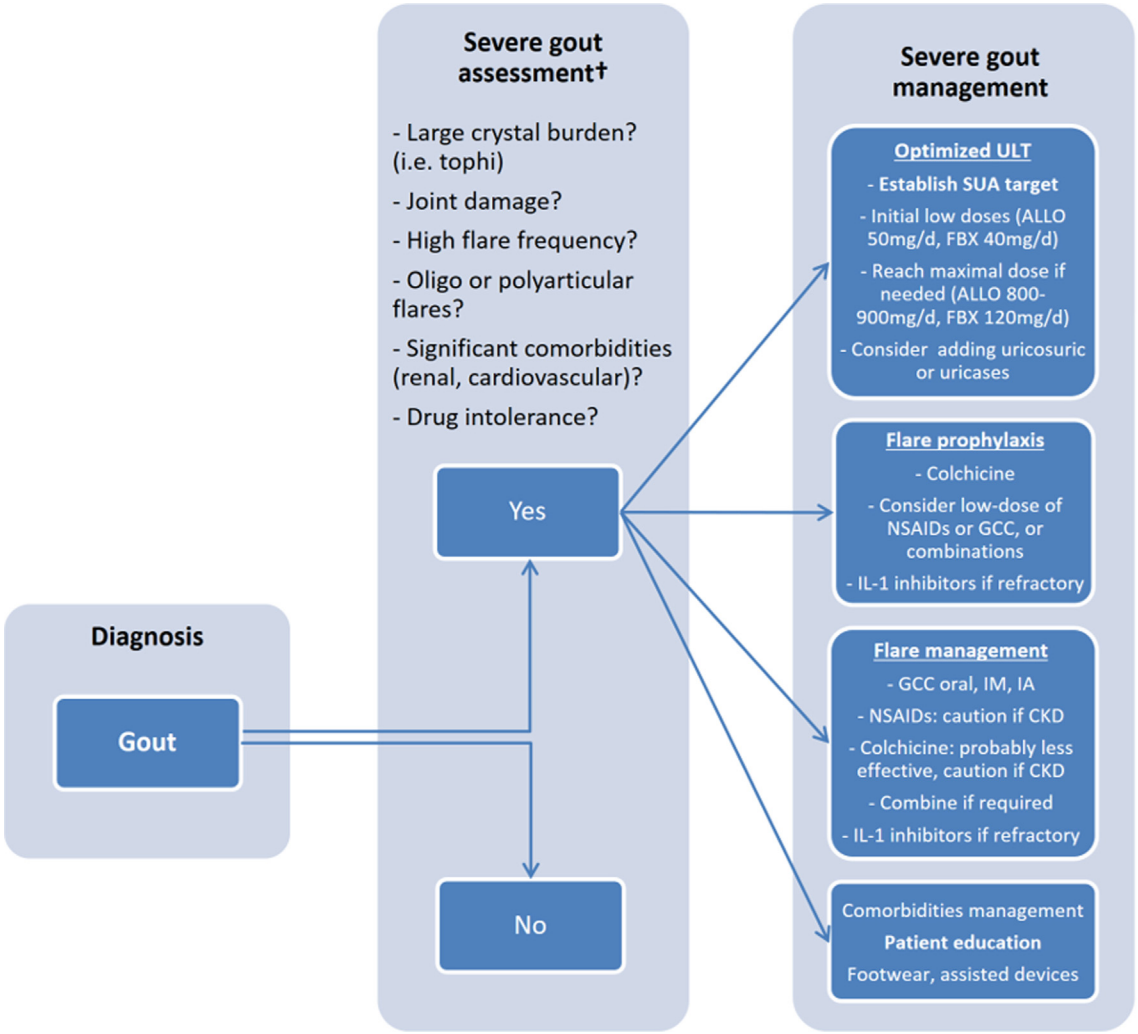

Fig. 2. Decision tree for severe gout assessment and management. ALLO: allopurinol; CKD: chronic kidney disease; FBX: febuxostat; GCC: glucocorticoids; IL-1: interleukin 1; IA: intra-articular; IM: intramuscular; NSAIDs: non-steroidal anti-inflammatory agents; SUA: serum uric acid; ULT: urate-lowering therapy. †Other features may also indicate severe gout.