EXTENDED REPORT

Treat-to-target (T2T) recommendations for gout

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ABSTRACT

Objectives The treat-to-target (T2T) concept has been applied successfully in several inflammatory rheumatic diseases. Gout is a chronic disease with a high burden of pain and inflammation. Because the pathogenesis of gout is strongly related to serum urate levels, gout may be an ideal disease in which to apply a T2T approach. Our aim was to develop international T2T recommendations for patients with gout.

Methods A committee of experts with experience in gout agreed upon potential targets and outcomes, which was the basis for the systematic literature search. Eleven rheumatologists, one cardiologist, one nephrologist, one general practitioner and one patient met in October 2015 to develop T2T recommendations based on the available scientific evidence. Levels of evidence, strength of recommendations and levels of agreement were derived.

Results Although no randomised trial was identified in which a comparison with standard treatment or an evaluation of a T2T approach had been performed in patients with gout, indirect evidence was provided to focus on targets such as normalisation of serum urate levels. The expert group developed four overarching principles and nine T2T recommendations. They considered dissolution of crystals and prevention of flares to be fundamental; patient education, ensuring adherence to medications and monitoring of serum urate levels were also considered to be of major importance.

Conclusions This is the first application of the T2T approach developed for gout. Since no publication reports a trial comparing treatment strategies for gout, highly credible overarching principles and level D expert recommendations were created and agreed upon.

INTRODUCTION

Gout is caused by deposition of monosodium urate (MSU) crystals within joints in the setting of chronic hyperuricaemia.[1] It affects 1%–2% of adults in developed countries and is the most common type of inflammatory arthritis worldwide. Epidemiological data are consistent with a rise in the prevalence and incidence of gout.[2 3] Nutrition and genetic polymorphisms of renal transporters of urate and other genes seem to be the main causal factors of primary gout. Gout and hyperuricaemia are associated with hypertension, diabetes mellitus, metabolic syndrome and renal and cardiovascular diseases.[1 4 5] There is a strong link between gout and increased risk of death from all causes and cardiovascular diseases.[6] The economic burden of gout is considerable.[7]

Gout is a common clinical problem encountered by both general and specialist clinicians. The key principles of gout management include establishing a definitive diagnosis, treating acute attacks promptly and using urate-lowering therapies (ULTs) appropriately to dissolve MSU crystals to eventually prevent further attacks and joint damage. When serum urate concentrations are lowered below the saturation point of MSU, new crystal formation is prevented, existing crystals dissolve and gout can be cured. The 'gold standard' diagnostic test for gout remains the identification of MSU crystals by polarised light microscopy in synovial fluid cells or in a tophus.[8]

Non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine remain the most widely recommended systemic drugs to treat acute attacks.[9 10] In some patients, especially those with comorbidities that preclude NSAID use, oral glucocorticoids (GCs) may represent an alternative. Joint aspiration and injection of GC is recommended where feasible, as in most hospital settings.[11–13] Patient education, appropriate advice regarding lifestyle and treatment of comorbidities are important in the management of patients with gout.[14]

Many different recommendations on the management of gout have been published over the last decades.[11–13 15–18] However, major questions, as discussed below, remain.[19–22]

In many areas of medicine, such as diabetes care or cardiology, clear therapeutic targets have been defined and the continuous effort to reach these targets is standard practice.[23–28] More recently, treatment targets have also been advocated for rheumatoid arthritis (RA), spondyloarthritides (SpA) including psoriatic arthritis (PsA) and systemic lupus erythematosus, namely remission or low disease activity.[29 30] These recommendations have been based on insights gained from systematic literature reviews (SLRs) of clinical trials.[31 32] The successful application of a treat-to-target (T2T) strategy in a rheumatologic disease was first reported in RA and subsequently in PsA.[33 34]

Much less information is currently available regarding the value of defining therapeutic targets for gout. Despite recently published treatment recommendations[11–13 15 17 18] and some scientific and therapeutic advances, such as the approval of the first selective urate transporter inhibitor, a variety of challenges, such as preventing recurrence

of attacks, remain when considering the current management of patients with gout. These challenges exist, in part, because a clear therapeutic target and strategies to reach such a target have not yet been defined optimally. To improve the management of gout in clinical practice, a core group was convened to discuss and develop consensus recommendations aimed at defining a treatment target and initiate a T2T programme for gout.

METHODS

Five rheumatologists from Europe and North America with expertise in gout met in Athens in April 2014 and agreed on the need to develop T2T recommendations for gout. A steering committee was established, comprised of rheumatologists who were identified based upon their expertise in gout, experience in developing treatment recommendations, publication record and participation in clinical trials of novel therapies for gout. Through face-to-face discussions and email communications, they agreed to use a four-step methodology:

(i) define treatment targets and outcomes
(ii) perform a systematic literature review (SLR)
(iii) evaluate the findings of the SLR within the steering committee
(iv) develop final recommendations for T2T for gout with a larger task force.

Definition of target and outcomes: The steering committee determined potential targets and outcomes by email communication. There was no limitation to the number of targets and outcomes that could be proposed. Each target and outcome was then voted upon by email communication using a Delphi method; those that were supported by at least 75% of the members were accepted.

Systematic literature review: Search terms for the SLR were formulated based on the PICO (participant intervention, control, outcome) system, taking into account the targets and outcomes (see online supplementary table S1). Authors UK and CF performed the SLR using Medline, EMBASE and Cochrane, focusing on strategy trials in which therapeutic adjustments were made according to prespecified timelines and/or prespecified endpoints. Detailed inclusion and exclusion criteria and the list of search strings are shown in online supplementary tables S1 and S2. All English language human studies were evaluated based on an iterative process with screening of titles, followed by screening of abstract and completed by a full-text review. The results of the SLR were graded for the level of evidence provided by the Oxford Centre for Evidence-Based Medicine on a scale of 1–5.[35] We did not exclude studies based on quality.

Evaluation: The findings of the SLR were presented to the steering committee at a meeting in Herne, Germany, in June 2015. On this basis, the steering committee formulated a provisional set of recommendations according to European League Against Rheumatism standardised operating procedures fulfilling the AGREE criteria.[36 37] The level of evidence and strength of each recommendation were determined and categorised as A (highest) to D (lowest) on the basis of the SLR. The preliminary recommendations were distributed to the international task force, which consisted of gout experts from North America, South America, Europe, Oceania (New Zealand) and Asia; a nephrologist, a cardiologist, a general practitioner and a patient with gout.

Development of final recommendations: The international multispecialty task force met in Herne, Germany, in October 2015, to discuss the T2T approach in detail and develop the final recommendations. The background of the T2T approach was discussed and the preliminary recommendations developed by

the steering committee were presented. These were reformulated and reordered, until each recommendation received a majority of at least 75% of the votes by using a nominal consensus technique. After the face-to-face meeting, the final recommendations were circulated by email to the entire task force for final comments. Only suggestions intended to improve the clarity of wording or to address redundancies were considered; no changes to the content were allowed at this point. The task force then voted by email on the level of agreement with each recommendation using a numerical rating scale of 0–10, with the highest value indicating the greatest level of agreement.

RESULTS

Definition of target and outcomes: Six possible treatment targets and five possible outcome domains were identified by the steering committee (table 1). The final list includes four targets and three outcomes about which a SLR should be performed.

Systematic literature review: Of the initial 761 papers retrieved, 55 were selected for full-text review. No randomised trial was identified in which a T2T approach had been evaluated in comparison with standard treatment (flow chart in online supplementary figure S1 illustrates the selection process). However, there was indirect evidence that optimal therapeutic approaches help to control the disease.[38–42] The investigators showed that control of serum uric acid levels (SUA) is optimised by providing patient education, enhanced telephone access to expert advice, upward titration of allopurinol, febuxostat or benzbromarone and increased frequency of visits until the target SUA concentration was achieved.[14] Other urate-lowering agents, such as lesinurad, might also be used but strategy trials employing these drugs were not identified in the SLR. Successful reduction of SUA levels by upward titration of ULT, but without prescheduled therapeutic adaptation processes, has been demonstrated in many other trials.[38–40 43 44] Patients with gout exhibited a higher velocity of tophus size reduction when reaching a serum urate concentration below the saturation point of MSU early and maintaining that level.[39 45 46]

Table 1 Voting on treatment targets and outcomes

	Agreement* (%)	Accept
Treatment targets		
Serum urate level	90	Yes
Time to resolution of inflammation	40	No
Amount/reduction/absence of tophi (burden of deposition)	90	Yes
Pain reduction	90	Yes
Prevention/absence of attacks	100	Yes
Adherence to medication	60	No
Outcome		
Clinical: Pain, joint count, number of attacks/year	100	Yes
Laboratory: Serum urate level, CRP, ESR, serum creatinine	90	Yes
Functional: SF-36 (physical component score)	60	No
Imaging: Radiographs (specific signs), ultrasound (tophi), dual energy CT (urate deposition)	60	No
PRO: QoL, SF-36, work status, productivity, work days off, absenteeism/presenteeism	80	Yes

*10 members of the steering committee voted.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PRO, patient-reported outcomes; QoL, quality of life; SF-36, short-form 36.

Recommendation

Significant discussion also focused on asymptomatic hyperuricaemia. Although intervention to treat severe asymptomatic hyperuricaemia has been recommended in Japan,[47] there is inadequate evidence to support its appropriateness. The task force members agreed that it could be valuable to develop an appropriate strategic approach to the treatment of asymptomatic hyperuricaemia. However, they concurred that there is no evidence to suggest that the treatment target for asymptomatic hyperuricaemia should be any different than that for gout.

Evaluation: Based on the SLR, preliminary recommendations (three overarching principles and eight recommendations) were formulated by the steering committee.

Recommendations: The preliminary recommendations were reformulated and reordered by the task force during a meeting in October 2015, yielding four overarching principles and nine recommendations. The final consensus recommendations are listed in table 2 and discussed in detail below.

Overarching principles

Since gout is a potentially curable disease, the central guiding principles are to reduce serum urate levels and to maintain a target serum urate level. To achieve these goals, patients must be educated completely about the disease and should participate in the decision-making process. The overarching principles, which are listed in table 2, address the following aspects:

A. Gout as a chronic and serious disease that can be treated effectively.[6]
B. The importance of reducing and maintaining serum urate below a defined target.
C. The requirement for patient education about all aspects of the disease and for shared decision-making with the patient.[14]
D. The need for long-term adherence to urate-lowering therapy.

Recommendations

The main points discussed were as follows:

(i) Both providers and patients should be educated about the disease and its treatment.

(ii) Patients and healthcare providers should make treatment decisions together.
(iii) The primary treatment approach is to reduce and maintain serum urate at a level sufficient to effect dissolution of MSU crystals.
(iv) Modifying lifestyle and monitoring renal function are important.

It was decided to not differentiate between 'acute' and 'chronic' gout, since both belong to the spectrum of a single disease.

All recommendations are presented in table 2 together with the level of supporting evidence, the strength of the recommendation and the level of agreement. Of note and in line with the SLR, the level of evidence was low (D) for most of the recommendations. This lack of evidence supporting how best to treat gout likely is one of the main reasons why it is often difficult to treat the disease successfully and especially to maintain patients free of disease activity over the long term. In the presence of comorbidities, such as renal impairment, the aim of low disease activity is much more complicated to reach which was the basis to recommend assessment of renal function on a regular basis. It also provides the basis for the research agenda, since much more information is needed to develop highly valid treatment recommendations.

Interestingly and despite the low level of evidence, there was a very high level of agreement among task force members, with six of the nine recommendations achieving agreement levels of 9.5 or more on a 10-point scale. This suggests that the experts from different fields and the patient with gout on the task force were quite convinced of the validity of the statements. Only recommendation #5, which deals with prophylaxis, had a lower level of agreement (8.3). This lower level of agreement was due to the absence of prospectively acquired data regarding the appropriate duration of prophylaxis.

A research agenda was also developed (table 3). It was decided to re-evaluate the current proposals at a future meeting attended by several stakeholders, including more patients. Therefore, the present recommendations should be regarded as a basis for further discussion and amendment.

Table 2 Recommendations to treat-to-target gout

		LoE	GoR	SoR
Overarching principles				
A	Gout is a chronic and serious disease with impaired quality of life and reduced life expectancy that can be treated effectively.			9.5±0.9
B	Reducing and maintaining serum urate below a defined target is mandatory to eliminate urate crystals and improve patient outcomes.	–	–	9.8±0.7
C	Successful management of gout requires education about all aspects of the disease and full involvement of the patient in shared decision-making.	–	–	9.7±0.7
D	Long-term adherence to urate-lowering therapy is essential for an optimal outcome.	–	–	9.4±0.8
Recommendations				
1	Serum urate must be measured regularly and urate-lowering therapy should be adjusted to attain the therapeutic target.	2	B	9.8±0.6
2	A serum urate level <6 mg/dL (<360 μmol/L) should be targeted and maintained in all patients with gout	1	A	9.5±0.9
3	In patients with severe gout, such as those with tophi or frequent attacks, the target should be a serum urate level <5 mg/dL (<300 μmol/L) until clinical remission is achieved	5	D	9.2±1.5
4	Acute attacks should be treated promptly with anti-inflammatory medications, taking safety issues into consideration	5	D	9.9±0.5
5	Prophylaxis against attacks should be initiated and continued for at least 6 months after starting urate-lowering therapy.	5	D	8.3±1.7
6	In all patients with gout, renal function should be assessed at the time of diagnosis and then monitored regularly.	5	D	9.6±0.7
7	Comorbidities associated with gout may influence therapy and outcomes and should be assessed regularly and managed	5	D	9.5±0.8
8	Modifiable risk factors should be addressed primarily through patient education and support.	5	D	9.2±1.5
9	Information about gout and its management should be made readily available to patients by their healthcare professionals.	5	D	9.7±0.7

SoR on a 0–10 scale with 0=no agreement at all and 10=very strong agreement.
GoR, grade of recommendation; LoE, level of evidence; SoR, strength of recommendation.

Table 3 Research agenda

No	Research question	Comment with respect to a T2T approach
1	What is the optimal target serum urate level to manage gout?	SUA level of <6 mg/dL (<360 μmol/L) or <5 mg/dL (<300 μmol/L) are not data driven, a valid and reliable cut-off will facilitate a targeted approach.
2	Is the current recommended target serum urate level a valid endpoint?	This important question should be addressed by taking the scientific evidence and the patient point of view into account. A laboratory parameter might not adequately reflect the signs and symptoms of the patient.
3	How often should the serum urate level be measured to optimally control disease?	Definition of time intervals to measure SUA is mandatory to adapt therapy based on the treatment target.
4	How does frequency of serum urate measurement impact on the management of patients with gout?	Frequency of measurements should be feasible and aim to avoid overassessment and underestimation. No trial exists at all to address impact of measurement on the management of patients with gout.
5	Are very low serum urate levels dangerous (such as by causing neuropsychiatric disease, eg, dementia)?	The knowledge about valid upper and lower thresholds of SUA is mandatory to follow a T2T approach.
6	What are the consequences of lowering serum urate levels?	A T2T approach in patients with gout must address potential harmful consequences (like occurrence of acute attacks while initiating ULT).
7	Is it possible to develop a composite disease activity measure that might serve as a better target for management of gout disease activity in clinical practice? (GDAI=gout disease activity index).	More than the SUA level influences disease activity in patients with gout. Therefore, it seems likely that a composite instrument is addressing the patients need more accurate.
8	Does an elevated serum urate level cause chronic kidney disease?	The relationship between gout and chronic kidney disease is bidirectional and whether it is a causal relation or an association is still a matter of debate. It still has to be shown that lowering of SUA prevents renal function from further deterioration (and vice versa).
9	How often should renal function be measured?	Frequency of measurements should be feasible and aim to avoid overassessment and underestimation.
10	What is the optimal management of gout in patients with multiple comorbidities?	Determination of treatment target and strategy to adapt the therapy depends on occurrence of many factors, that is comorbidities. Multidisciplinary management should agree upon an achievable treatment target.
11	Is there any diagnostic utility to aspirating joints in patients with intercritical gout?	The absence of crystals in the synovial fluid is one of the targets that are linked to lowering SUA. Serial joint aspiration studies confirmed the disappearance of crystals with effective ULT. The value of this laboratory finding in patients with absent of gout attacks is questionable.
12	Should monitoring by ultrasound or CT be used in gout?	Diagnostic utility of imaging procedure has been studied to diagnose but has not been extensively studied to monitor the disease. Since deposition of MSU crystals in the tissue is a consequence of increased levels of SUA imaging procedure might serve as a surrogate marker in the management of gout.
13	How is the treatment of both acute and chronic manifestations of gout best integrated into a T2T strategy?	Whether the artificial partition between acute and chronic stages is helpful in treating patients with gout is still a matter of debate. However, research on implementations strategies focused on setting a target and adapting the treatment accordingly is strongly needed.
14	What is the optimal timing of initiating treatment for acute gout attacks?	The start of the treatment and prescheduled adaptation process within the treatment strategy is a crucial point that is not yet well defined in studies. Especially, initiating ULT during an acute gout attack remains a matter of debate.
15	What is the optimal strategy to eliminate tophi?	The outcome 'size and number of tophi' is difficult to assess. There is no consensus about the optimal tool to assess this outcome reliable and sensitive to change. However, assessment of tophi is crucial to assess adaptation process within the treatment strategy.
16	Should urate lowering therapy be initiated after the first gout attack?	Whether ULT therapy should be initiated after the first gout attack or after a subsequent attack remains controversial. Studies should be conducted to address this question, so as to optimise treatment
17	Is there any effect of treating asymptomatic hyperuricaemia?	Studies are warranted to assess whether T2T approach is also applicable for patients with asymptomatic hyperuricaemia.
18	What is the role of surgery in the treatment of tophi?	Pharmacological interventions are the cornerstone in the T2T approach, but the value of surgical procedures has not been investigated.
19	Does a T2T approach improve the adherence of patients to their treatment?	Adherence to treatment is low in patients with gout. In a T2T approach, patients do have increased visits at least in the beginning of their disease. One important question is whether this approach is increasing the adherence of patients to their treatment

MSU, monosodium urate; SUA, serum uric acid levels; T2T, target-to-target; ULT, using urate-lowering therapy.

DISCUSSION

This is the first initiative to propose overarching principles and recommendations for the management of gout using a T2T strategy. Since this approach has been applied to several other rheumatic diseases,[29] [30] we considered it important to employ this successful concept in gout—a disease for which a major target can be defined easily and in which outcomes depend upon maintenance of the serum urate concentration at a low level. However, the scope of the recommendations is focusing on targeted treatment options and on a broader concept including recommendations for prophylaxis against attacks and monitoring of comorbidities. This rationale is based on the fact that aiming for low serum urate concentrations must be supported by anti-inflammatory strategies and/or prevention of comorbidities.

After discussion about asymptomatic hyperuricaemia, the group decided not to make recommendations regarding treatment of hyperuricaemia in the absence of musculoskeletal symptoms because of inadequate evidence. One major concern, which was raised during this discussion, was that treatment targets for asymptomatic hyperuricaemia need to be defined. Further research on this topic is warranted and should be conducted in collaboration with cardiologists and nephrologists.

A T2T approach is based on assessing disease activity or severity. Neither is defined for patients with gout. The term 'severity' is inexact when referring to patients with gout and reflects a variety of parameters, such as frequency of attacks, number of swollen joints, number and size of tophi and presence of comorbidities. No threshold has been defined to differentiate between severe and mild disease states. Some progress has been made in establishing disease activity scores for gout. Recently, the KING study group proposed a new disease activity score for gout including flare, SUA, pain, global activity assessment, joint count and measure of tophi.[48]

However, assessment of outcome domains is not yet standardised in trials with gout patients. Several processes have been implemented within OMERACT to endorse measures of outcome. Pain, joint count and patient global assessment are the recommended outcome measures for patients with acute gout, whereas these three outcome measures with the addition of activity limitation are the outcome measures recommended for patients with chronic gout.[49 50] There is sufficient evidence to support measures of pain, joint tenderness and swelling as fulfilling the requirements of the OMERACT filter.[51] However, almost no appreciable impact of the OMERACT-proposed domains could be detected in our SLR.[52]

Initially, we discussed possible treatment targets that should be able to reflect when patients are in remission. The final target list includes pain and SUA levels, as well as the absence of attacks and tophi, as potential parameters to define remission in patients with gout. Remission as a separate variable was not included in our list of treatment targets because no formal decision has yet been made about the set of variables proposed by OMERACT in 2014 to define remission. The publication of preliminary remission criteria for gout in 2016 supports the OMERACT group's recommendation of variables to define remission.[53]

Because of the lack of strategy trials in gout, existing therapeutic recommendations are rather vague. For example, clinicians need guidance regarding the strategic use of anti-inflammatory medications to balance potentially beneficially and harmful effects in patients with acute attacks. However, T2T recommendations are primarily generic in nature and do not provide detailed management recommendations or focus on specific drugs. Although some drugs are mentioned as examples, the current recommendations do not endorse one drug over others. With respect to the use of anti-inflammatory medications, our task force was not able to propose a specific sequence of anti-inflammatory medications because trials to address this question were never performed. Therefore, we propose a research agenda to stimulate investigation into the unmet needs in this area, including evaluation of the validity of a T2T strategy in gout. This research agenda includes those questions that were considered to be most important by the task force, but the list obviously could be expanded in many areas, including molecular aspects of pathophysiology and patient and physician considerations.

This represents the first initiative to characterise gout as a disease that should be managed by defining, achieving and maintaining a treatment target to provide patients with the best possible outcome. Its strengths are the inclusion of experts from different areas of medicine and a gout patient representative on the task force and the very high level of agreement that was achieved for most of the recommendations. However, the present activity was limited by the absence of published clinical trials of strategies to treat gout. Thus, recommendations had to be developed based solely upon expert opinion. Another limitation of our approach might be our having limited our SLR to only articles written in the English language. The prevalence of gout and the need for a targeted therapeutic approach is also increasing in less developed countries, such as those in Latin America and in parts of Asia.[2]

Further research is needed to apply our T2T recommendations in a clinical trial, comparing target-directed therapy with routine care. The research agenda addresses many practical questions, such as determining the frequency with which critical blood tests should be performed, assessing the impact of comorbidities and developing a gout disease activity index. Given the low adherence to medication by patients with gout, strategy trials, in which therapeutic adjustments are made according to a prespecified timeline and/or prespecified endpoints, should address this critical issue. Presumably, strategy trials will be able to include an adequate approach to control for non-adherence.[54] A treatment strategy study will be important to improve the management of patients with gout and should be initiated in the near future.

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