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Review

Rational pharmacotherapy (RPT) in goutology: Define the serum uric acid target & treat-to-target patient cohort and review on urate lowering therapy (ULT) applying synthetic drugs

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ABSTRACT

A gout revolution is at hand as can be seen from the number of publications and our recent increase in a better understanding of gout regarding imaging, regarding pathogenetic involvement of crystals, cells and cytokines, as well as regarding new pharmacotherapeutic options. We should now focus on rational pharmacotherapy to significantly improve gout care. With modern combinations of xanthine oxidase inhibition PLUS uricosuric all serum urate concentrations can be targeted. The pharmacotherapeutic literature of synthetic urate lowering treatment is reviewed and a plea is given for rational pharmacotherapy combining different modes of action aiming at the rheumatologically predefined optimal serum urate concentrations instead of a more reluctant approach to just lower a serum urate to any lower level with a fixed dose allopurinol.

1. Introduction

After decades of having been the sleeping beauty of rheumatology recent developments in gout prove goutologists have been kissed awake. Novel developments are revolutionary and reflect a huge acceleration in our understanding of gout. Newer applications of imaging by ultrasonography (US) and dual-energy CT-scanning (DECT), insight into innate immunity in association with novel pharmacotherapeutic options such as interleukin-1 inhibitor canakinumab and a new purine nucleoside phosphorylase inhibitor (PNPi) ulodesine (phase 2)/xanthine oxidase inhibitor (XOi) febuxostat (already EMA/FDA granted)/uricosurics (US) lesinurad (phase 3) and experimental RDEA3170 are product as well as driver of this revolution. Currently, science goes by modern rules of evidence-based medicine, with powerful studies answering predefined questions. In the field of pharmacotherapy pharmaceutical companies often aim to invest at studies proving superiority of a novel medication versus an older one in order to get registration, nearly always in a monotherapy setting, and possibly in a suboptimal dose of the older XOi allopurinol. Some of the more recent studies are into combination therapy where any novel ULT drug is combined with allopurinol, since XOi is supposed to be the cornerstone of gout pharmacotherapy. What is the role we as professionals wish to play? If authorities and pharmaceutical companies predominantly pose superiority questions of monotherapies we should define the current research agenda, particularly since we know all serum urate levels are within range and thus can be targeted by clinicians.

In metabolic diseases with urate accumulation it is rational from a mechanistic point of view to aim for inhibition of urate production to a certain degree. If predefined stringent targets cannot be reached we should aim for additional urate excretion, in the absence of contraindications. This particularly goes for gout in which renal underexcretion is a predominant factor. Many studies so far go into head-to-head comparison of production inhibitor A versus another production inhibitor B solely aiming at a biochemical target, never measuring excretion, the possible target of uricosurics [1,2]. Why not go for the rational principle to combine two different modes of action and go for a more potent strategy: for example add a production inhibitor to an excretion stimulator [3–5]. I here wish to elaborate on questions that are rational in individual patient care but were hardly posed over the last decades in studies. In individual cases many rheumatologists have done so for years, at least in countries where uricosurics (US) are available. Supposing that with optimal pharmacotherapy one may find an elegant balance of adequate effects with minimal dosages i.e. at low risk for serious adverse events. If this research is not done effective pharmacotherapies may be taken off the market by authorities without adequate

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arguments [6,7]. Therefore, we do need to answer the following questions:

- which is the optimal urate lowering therapy (ULT) to start with?
- which is the optimal combination ULT to being/remaining attack free?
- which is the optimal monotherapy ULT in the maintenance phase?
- which is the optimal serum urate concentration we should aim for?

2. Optimal serum uric acid (SUA)

Several studies of date, have previously suggested an U-shaped optimum of mortality and/or cardiovascular risk versus SUA: the lower as well as the higher SUA concentrations are associated with an increased CV risk. Recent findings from a hospital setting where the 1-year mortality increases with SUA > 0.36 mmol/L (6 mg/dL) as well as mortality increases with SUA < 0.24 mmol/L (4 mg/dL): the optimum region about 0.30 mmol/L [8]. This is still to be demonstrated in a population of gout patients, while on ULT.

3. Adding US to an XOI

Conceptually, an additive SUA lowering effect has to occur with the combination of two different modes of action i.e. production inhibition (XOi) PLUS stimulated excretion (US). As clinicians we are practicing rational pharmacotherapy on day to day base with individual patients and may have to combine many pharmacotherapies even though some combinations are so-called “off label”; according to updated benzbromarone 1B text benzbromarone is available in some European countries under strict restrictions, i.e. reserved for those patients intolerant for allopurinol. This has been stated by authorities without clear data support from literature, just focusing at reducing the number of patients at risk for benzbromarone-associated SAEs. In individual patients with inadequate lowering of SUA we often combine XOi and US. But data from large studies are lacking, only data from a small, short-term cohort study supports the combination of two different modes of action [5]. As clinicians we have to clear the road for novel medications, and offer our help in registration studies if they may result in improved therapy for the gout patient. But the knowledge we gather from (pivotal) trials should now fill the gaps needed for good clinical daily practice [4].

4. Rational pharmacotherapy (RPT)

The World Health Organisation (WHO) defines, rational pharmacotherapy (RPT) as a process of treatment in which patients receive medications appropriate to their clinical needs, in doses that meet their individual requirement(s), for an adequate period of time, and at the lowest cost to them and the community [9]. Multiple factors can be encountered that may well lead to irrational use of drugs [10]. Clearly, inadequate information and training of health workers are major factors of irrational drug use [11]. Thorough knowledge of both disease and pharmacological properties of drugs is needed. Regarding gout we need to understand the metabolism of urate, causes for urate accumulation, as well as the secondary response of the inflammasome and the interplay we can offer with pharmacotherapy.

5. What does RPT mean to gout?

In RPT, mechanism-based pharmacotherapy combines different modes of action resulting in a more effective strategy, at least theoretically. Thus, with RPT we may well target lower SUA levels easier and this should become visible with a more rapid debulking from urate mass, inability to form new crystals, rapid correction of inflammasome arousal and possibly early normalizing of cardiovascular risk in gout patients.

5.1. Prevention of crystals

Clinically gouty arthritis has a demonstrable cause: mono sodium urate (MSU) crystals, see Fig. 1. These MSU crystals may develop in patients with an elevated serum uric acid (SUA) caused by a positive urate balance. A negative urate balance will ultimately result in lower SUA levels, preventing urate accumulation and formation of MSU crystals.

5.2. Offset thermostatic regulation of inflammasome

In vitro studies showed the synergistic effect between free fatty acids and MSU crystals resulting in arousal of the inflammasome [12]. The interplay between the SUA and arousal of the inflammasome is to be cleared yet. This interplay may help us pointing towards the optimal SUA levels.

For years a rational approach in gout, even though renal underexcretion is a predominant cause, has been the treatment of a stable uniform dose of xanthine oxidase inhibitor (XOi). Currently, this still is reality in many parts of the world. A uniform fixed dose is even comparator of novel therapies in important trials: 300 mg allopurinol daily [1,2].

A more rational approach is based on the principle of treat-to-target (T2T) assuming that SUA < 0.30 mMol/L (as stated in the BSR guideline) should be targeted if feasible individually at all. Feasibility focusing on availability of medication and individual toleration of the medication. This may result in a step-up approach of first dietary measures and addition of a urate production inhibitor, and at a certain stage (not having reached the predefined target) the addition of a uricosuric (US). However, the clinical target for patients and some clinicians may be just being attack free, which per se can be reached in many by monotherapy 300 mg allopurinol and/or a colchicin regimen. Immunologically it may be better to aim for a more rapidly normalization of the immunologic arousal.

The easy target may be the biochemical serum urate concentration, which is the king of surrogate markers. SUA can be measured everywhere and is associated with all sequelae we know from

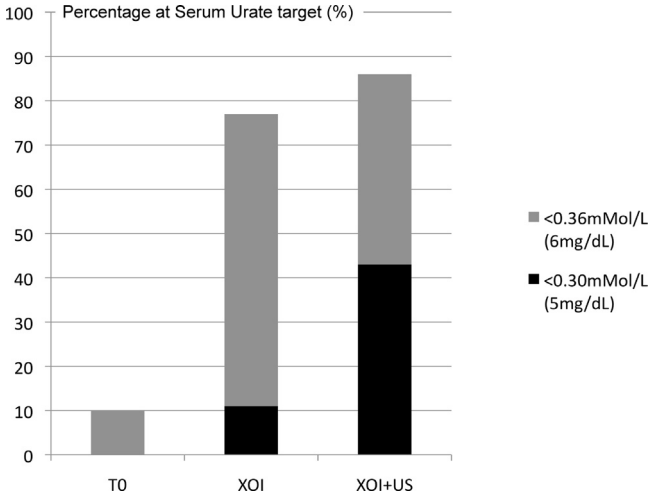

Fig. 1. Percentage of crystal-proven gout patients at several stages of therapy: T0 acute arthritis with proof of crystals; xanthine oxidase inhibitor (XOi) in equilibrium with 300 mg allopurinol daily (for at least 8 weeks); XOI + uricosurics in equilibrium with 300 mg allopurinol plus 100 mg benzbromarone daily (for at least 8 weeks).