Treat to target in gout by combining two modes of action

Targeting serum uric acid

This editorial refers to Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat in gout patients with hyperuricaemia, by Roy Fleischmann et al., doi:10.1093/rheumatology/ket487, on pages 2167–74.

Gout has become a hot topic since we improved our understanding of the inflammasome, improved our imaging modalities and last, but not least, have received new pharmacotherapeutic options in changing the urate metabolism. So far, pharmacotherapy of synthetic urate lowering treatment (ULT) often consists of an approach to just lower serum uric acid (SUA) concentrations to any level by prescribing a fixed dose of allopurinol, 300 mg/day. Some colleagues treat to a predefined target and prescribe allopurinol in escalating doses up to 900 mg/day. With the newer combinations of different modes of action, an SUA target of $<0.30 \text{mmol/l}$ in almost all patients has become feasible; this has been demonstrated by Fleischmann et al. [1] in this issue of the journal.

In urate accumulation it may be rational, from a mechanistic point of view, to start by inhibiting urate production. If the predefined lower SUA targets cannot be reached one may consider adding a stimulator of urate excretion, a uricosuric, or even a second production inhibitor of purine nucleotide degradation (see Fig. 1) [2]. In advanced, tophaceous gout it has previously been demonstrated that the lower the SUA, the higher the velocity of tophaceous size reduction [3]. Pivotal trials with febuxostat compare monotherapy with the production inhibitor allopurinol vs monotherapy with the production inhibitor febuxostat [4, 5]. At least two options to improve biochemical urate lowering efficacy may be explored. Measurement of serum concentrations of the active drug may enable optimization of treatment, i.e. therapeutic drug monitoring. Measuring the urate excretion may be helpful to identify patients who could benefit from uricosurics. Modern ULT also offers opportunities for the combined use of two production inhibitors, such as a xanthine oxidase inhibitor (XOI) plus a urate nucleotide phosphorylase inhibitor, i.e. aludesine [2]. Having these pharmacotherapeutic options pushes us to question our current pharmacotherapy rationales and optimal cost efficacy. The answer may be to combine the use of two different modes of action if biochemical targets have to be reached [1–3, 6].

Pharmacotherapy decisions start with feasibility assessments of these lower targets: is prescription of an increased allopurinol dose or addition of benzbro- marone/probenecid feasible in your country? Clinicians then need to be convinced that this is the right way to treat their patients. If convinced, they then need to convince patients to take these additional medications. However, clinicians will only be willing to treat aggressively in the initial (or maintenance) phase when a consensus/guideline exists, preferably one based on evidence such as improved prognosis and lower attack rates. Furthermore, questions must be answered on the duration of the lower SUA targets: is it needed for a 1-, 2- or even 5-year period or is it lifelong? If not properly addressed, problems regarding patient non-adherence will persist. Socio-economically, combination therapy means additional costs for these combined prescriptions for a substantial population of gout patients. Could this treatment result in less absenteeism from work or fewer admissions? Many questions need to be answered now that we know these lower SUA targets are feasible [2].

The question of an optimal SUA depends on the outcome measures: attack rate, urate debulking or cardiovascular mortality. Mortality is most appealing, as several studies have previously suggested a U-shaped mortality vs SUA curve: the lower as well as the higher SUA concentrations are associated with an increased mortality risk [7]. This is yet to be demonstrated in a population of gout patients using ULT. With ULT, the lower SUA levels are associated with more rapid debulking, and possibly with a more quiescent inflammasome [3, 8].

Conceptually, an additive SUA lowering effect has to occur with the combination of two different modes of action, i.e. a production inhibitor (XOI) plus a uricosuric such as blocker of urate transporter 1, organic anion transporter (OAT1, OAT3 or OAT4) and/or glucose transporter 9. In individual patients, clinicians will combine pharmacotherapies on day-to-day basis, even though some combinations are called off-label. According to the updated benzbromarone 1B text, benzbromarone is available in some European countries under strict restrictions, i.e. reserved for those patients intolerant of allopurinol. This has been stated without clear support from the literature. Fleischmann et al. [1] are the first to demonstrate a superior urate lowering effect with the combined use of febuxostat plus lesinurad.
Gouty arthritis has a demonstrable cause: monosodium urate (MSU) crystals. These MSU crystals may develop in patients with elevated SUA caused by a positive urate balance. A negative urate balance will ultimately result in lowering of SUA levels, preventing urate accumulation and resolution of MSU crystals inducing debulking [3].

In vitro studies have shown the synergistic effect between free fatty acids and MSU crystals resulting in arousal of the inflammasome [8]. Lower SUA may lead to an offsetting of inflammasome activity. Along with epidemiological data, this interplay may help us to define the optimal SUA level.

Urate overproducer and urate underexcretor were used in the past to find an indication for uricosurics. Nowadays these measurements may have importance in genotyping aimed at finding genetic polymorphisms in gout populations.

A uricosuric added to an XOi induces a significant increase in urate excretion that can be measured in urine [9, 10]. The uric acid urine:plasma ratio is unchanged with or without an XOi and will increase significantly when benzbromarone is added to allopurinol. This ratio can be divided by a creatinine urine:plasma ratio, resulting in a fractional clearance of urate (FCU). This FCU may be considered a phenotypic measure of the ability to clear uric acid, which in many gout patients is suboptimal [10].

Trials have shown the value of allopurinol as an initial ULT in gout, but if not tolerated, the efficacy of febuxostat is indisputable [4, 5]. Benzbromarone 200mg/day is biochemically equipotent to allopurinol 600mg/day or febuxostat 80mg/day, all in monotherapeutic settings. The combined targeting of two different modes of action has superior urate lowering effects, so now everything is possible.

Disclosure statement: T.L.J. is a member of advisory boards for AbbVie, BMS, Janssen, Menarini Italy, Merck, Pfizer and Roche and has received funding for research in RA from AbbVie and UCB.

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