The Real World of Gout

Gout is a common cause of acute painful arthritis with a prevalence of 3.9% of adults in the United States, affecting an estimated 8.3 million people[1]. Gout prevalence increases with age, affecting 12.6% of those aged 80 and over[1]. Untreated and undertreated gout progresses to a chronic disabling arthropathy in a significant number of patients[2]. An increasing proportion of patients with gout have complex profiles of comorbidities and long prescription medication lists further complicating their management[3].

In this setting the recent publication of the American College of Rheumatology (ACR) guidelines for the management of gout are a welcome addition to the resources at the disposal of practicing clinicians to assist in the management of this group of potentially complex patients[4,5]. The ACR guidelines recommend probenecid as an alternative first-line pharmacological urate-lowering therapy for those with a history of contraindication or intolerance to a xanthine oxidase inhibitor and with a creatinine clearance of 50 ml/min or more[4].

Probenecid is a uricosuric agent that lowers serum urate by inhibiting renal tubular reabsorption of uric acid. Probenecid is infrequently prescribed as a urate-lowering therapy in many parts of the world including the United States and Europe[6,7]. The study reported by Pui, et al in this issue of The Journal is of considerable interest[8].

Pui, et al report their real world experience of probenecid usage in 57 patients attending a rheumatology clinic in New Zealand. The proportion of patients receiving probenecid was relatively high, at 10.9%, perhaps influenced by the present lack of availability of febuxostat in this market. The population described appear to have difficult-to-treat gout, with a high proportion (60%) with tophaceous gout and a mean baseline serum urate of 600 μmol/l. Half the patients started probenecid because of inadequate serum urate control while taking allopurinol (albeit at a mean dose of 362 mg); in these patients mean serum urate on allopurinol treatment was 500 μmol/l. The mean probenecid dose used in the study of 1.1 g is below that used in previous studies, for example the 2 g dose in the study by Reinders, et al[9].

The decrease in serum urate level in this study was moderate, with a 29% reduction with probenecid monotherapy and a 39% reduction with combination therapy with allopurinol. Thirty-five percent of patients achieved a serum urate concentration of < 360 μmol/l, an important target goal in the treat-to-target era. Interestingly, the authors included 15 patients (26%) with estimated glomerular filtration rate (eGFR) < 50 ml/min /1.73 m^2, but there was no increased risk of adverse events in these patients at the doses of probenecid used in the study, and the decrease in serum urate was similar to the group with normal renal function.

It is worthwhile to compare this study with previous randomized controlled trial (RCT) evidence of the efficacy of probenecid. Reinders, et al demonstrated a 50% reduction in serum urate with a 2 g/day dose of probenecid after failure of allopurinol therapy (due to intolerance or failure to achieve a serum urate of 300 μmol/l or less). In addition, 65% of probenecid-treated patients in this study achieved a serum urate concentration of 300 μmol/l or less. Again, these patients would be regarded as having difficult-to-treat gout, with a mean serum urate concentration of 540 μmol/l, and 54% having tophaceous gout[9]. The greater decreases in serum urate achieved by Reinders and colleagues are most likely explained by the higher probenecid doses used and the stringent environment of the RCT. Studies reporting real-world experience with medications are complementary to RCT and contribute to progress in clinical decision making.

The attitude that the RCT is king and all others must bow before it is pervasive in the medical world. In reality, each methodology has its strengths and weaknesses and truly informed "evidence-based medicine" must draw on all flavors of research study. Proponents of the evidence-based medicine approach to clinical practice often refer to a hierarchical ranking of study methodology based on internal validity; in other words, how correct study results are[10]. RCT, considered the gold standard of research methodology, have been shown to have the potential to

exhibit considerable heterogeneity of results[11]. The strict inclusion and exclusion criteria of most RCT have the potential to limit the generalizability of their results to patients commonly seen in clinical practice. In addition, the rigorous and frequent study visits often create an atmosphere and time investment that is not reproducible in a busy clinical practice.

Categorizing studies according to research design and judging their validity solely on this basis is a flawed ideology: many factors other than study methodology have the potential to introduce bias, limit generalizability, and make a study less useful to practicing clinicians. Other scientific disciplines have been more willing to accept the flaws of a rigid hierarchical view of research design and we can and should learn from experience in these fields[11].

A number of real-world studies of gout treatment have been reported. Allopurinol is a treatment in which the interpretation of RCT data have proven particularly difficult. In the setting of RCT, allopurinol is typically prescribed at a fixed dose of 100 to 300 mg, and is only infrequently dose-titrated based on serum urate levels, as would be the case in real-world clinical practice. This can lead to misinterpretations of the efficacy of allopurinol, if, for example, RCT of allopurinol versus febuxostat are taken at face value. RCT data on the efficacy of allopurinol typically demonstrate 21 to 46% of patients achieving a serum urate < 360 μmol/l[12,13]. In real-world clinical practice settings with titration of allopurinol dosage, the percentage of patients achieving target serum urate levels < 360 μmol/l increases to 58% to 100%[7,14]. Benzbromarone has been shown to have an efficacy of 78 to 92% for achieving a serum urate < 300 μmol/l in RCT, which increases to 100% in non-randomized settings[14]. Febuxostat has an efficacy of 53 to 94% for achieving a serum urate < 360 μmol/l in RCT[12,16]. To my knowledge there are scarce published data on the real-world efficacy of febuxostat. There are multiple subtleties in interpretation of real-world data: Findings are not as "clean" or as easy to interpret as RCT data. A cursory reading of the real-world data above would suggest that allopurinol may not be as effective as benzbromarone; however, closer examination will show that there are different degrees of "realness" and that in similar settings both agents have similar efficacy.

The integration of data from real-world clinical practice settings with RCT data provides the practicing clinician with an expanded resource of evidence with which to make optimum treatment decisions for individual patients. The increased time investment needed to properly evaluate observational studies may seem to be an obstacle; however, the time spent can be rewarding. Let's forget the old maxim: "If you find that [a] study was not randomized, we'd suggest that you stop reading it and go on to the next article" and evaluate studies on their own merits[17].

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