



## Editorial

### Gout: past, present, and future

### Gota: pasado, presente y futuro

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#### Past

Gout has been an exemplary disease insofar as how we perceive the large amount of academic knowledge we have about it. However, when systematic reviews of evidence were carried out, we found that gaps in knowledge were great and that empiricism has guided clinical practice to a great extent.<sup>1</sup>

Several examples can illustrate this statement. We lacked knowledge on renal urate transporters with regards to pathophysiology, taking into account that the majority of gout patients showed inadequate renal excretion of uric acid, whether primary or secondary. We were unaware of the key inflammation mediators in crystal arthritis, not only in acute but also in chronic. We knew about only the pharmacodynamic mechanism of allopurinol, although for about the last 50 years we suspected that uricosuric agents interacted with a renal transporter. During this time, paradoxically, it was claimed that diuretics induced hyperuricemia due to circulating volume contraction and glomerular filtration or tubular flow reduction.

With regards to diagnosis, the difference in agreement between observers and laboratories led to questioning whether diagnosis based on crystal observation in biological samples could be considered as the “gold standard.”

We had few well-designed clinical trials for non-steroidal anti-inflammatory drugs (NSAIDs) and no comparative study for corticoids in patients with episodes of acute inflammation. We did not know which drugs or with which dose optimal prophylaxis was achieved and even how long they should be maintained. Prophylaxis with NSAIDs was completely empiric, as there were no studies that would vouch for their efficacy or safety. The quantification of urate deposit was based on the presence of changes in simple x-rays and the presence of subcutaneous nodules compatible with tophi in the physical examination.

The treatment of hyperuricemia did not come out better off. Until 1999, when the first random trial with allopurinol was published,<sup>2</sup> we

lacked information on the efficacy of high doses of allopurinol, except for a few open studies, among which very few were comparative.<sup>3</sup> Uricosuric agents were rarely used, with a supposedly high risk of causing kidney stones and it was empirically recommended that patients should take alkalis to achieve a urine pH above 6. These uricosuric drugs were also demonised in all text books and reviews for supposedly not being effective in patients with slight to moderate renal failure.

Finally, when considering outcomes, we did not know whether a patient's self-reported gout attack was reliable. No physical or imaging method had been validated to measure tophi and there was disagreement among experts in setting a uricemia cut-off point as a target for hypouricemic treatment.

#### Present

In the last 10 years, the growth in knowledge concerning gout, taking the number of publications and communications in EULAR and ACR as a reference, has been exponential. However, there are still some who see those of us who are interested in this field as an “extinct species” formed by an “aged group whose interest is marginal to the majority of rheumatologists.”<sup>4</sup> Recent epidemiological studies in the last decade have allowed identifying the gout factors that relate to incidence and greater prevalence, as well as establishing an association between gout, not just hyperuricemia, and cardiovascular risk.<sup>5</sup>

Identification of the main tubular urate transporters, such as hURAT1 and Glut9,<sup>6</sup> has facilitated not only improving knowledge on the mechanisms that induce uricemia, but also a better understanding of the pharmacodynamics of uricosuric drugs and targets for future pharmacological actions. The NALP3 inflammasome pathway and IL-1 production seem to be crucial as mediators not only in acute but also in chronic inflammation induced by microcrystals.<sup>7</sup> This means a new, especially interesting, therapeutic target for the treatment of patients with extensive urate crystal deposit, for both prophylaxis and to control chronic inflammation.

Diagnosis based on the visualisation and identification of urate crystals with an optic microscope has fortunately become a recommendation not only for clinical practice<sup>8</sup> but also for patients to

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be included in trials for chronic gout.<sup>9</sup> The concordance in diagnosis and identification has shown to be excellent after training and suitable standardisation of the procedure.<sup>10</sup>

The development of the gout study group in OMERACT has facilitated the validation of several outcome measures. These, although perhaps primarily designed for use in clinical trials, may be applied extrinsically in clinical practice, such as uricemia and the measurement of subcutaneous tophi with callipers and joints with imaging techniques.<sup>11</sup> A study of acute inflammation episodes in patients with gout—with a positive diagnosis—states that the self-diagnosed gout attack associated with a visual analogical scale of pain by a chronic patient is as reliable as an expert's clinical assessment.

We have the first double blind, masked, parallel trials specifically designed for gout, comparing the new NSAID drugs (etoricoxib, lumiracoxib, celecoxib). The first trial compared “low” doses of colchicine with “normal use” doses, together with a first trial comparing NSAIDs with glucocorticoids.

The trials for the clinical development of febuxostat have allowed us to establish prophylaxis time: at least 6 months in patients without tophi and at least one year in patients with tophi. When the prophylaxis was maintained for 6 months, less than 5% of patients without tophi showed acute inflammation episodes during the year, while 30% of patients with tophi still suffered acute inflammation episodes. However, we still do not know the efficacy and safety of NSAIDs in prophylaxis, or the minimum dose of colchicine that should be prescribed to attain effective prophylaxis.

A new drug has been authorised by the EMA and FDA for hyperuricemia treatment in patients with gout (febuxostat) and pegloticase has recently been approved by the FDA. Methods for the classification, selection, risk assessment of kidney stones and monitoring of patient treatment with uricosuric drugs have also advanced.<sup>12</sup>

However, it is not all good news. The variability in handling gout is great, especially when referring to diagnosis and uricemia control in the long term.<sup>13</sup> We have sufficient evidence to confirm the speed that urate crystal deposits are reduced, which is opposite to that found in uricemia levels during treatment.<sup>14</sup> We still have an important lack of information regarding prescribing, handling and safety of the drugs that are currently available.

We do not have a technical file on benzbromarone. The one from January 2011 on colchicine is so restrictive that it will probably not be used except for prophylaxis; and that of allopurinol is, in my opinion, even less precise.

The only information available on benzbromarone is the 2004 AEM note referring to the restriction of its use and the withdrawal of its commercialisation in medications that contained combined allopurinol and benzbromarone. In the note, its indication for asymptomatic hyperuricemia in patients with renal failure is accepted, but its use is restricted in patients with gout to those with severe gout (polyarticular and tophaceous) and adverse effects or inefficacy with allopurinol. However, they do not mention the possibility of its use when benzbromarone is combined with allopurinol. It strikes us that before allopurinol treatment failure, and until febuxostat is available, benzbromarone can be prescribed for any patient with gout (and hyperuricemia) and kidney failure, but not for a patient with monoarticular or oligoarticular gout or without tophi and who has normal kidney function. This situation would lead us to recommend to this last patient: Come back tomorrow: develop tophi or oligoarticular gout and then I will have, *lex artis*, an indication to be able to treat you with benzbromarone!

Allopurinol is something else. We lack long-term follow-up studies with doses greater than 300mg/day to assess its safety. There are few open series and only one trial where 13 patients were exposed to doses of 600mg during 2 months! Although it is recommended to correct the doses depending on renal function level,

the recommendations for use are probably conservative and lead to an insufficient correction of uricemia in a great number of patients. The technical file of allopurinol in Spain<sup>15</sup> is illustrative: the range of approved doses varies between “2 and 10 mg/kg of body weight/day”—Does that mean up to 1,000 mg in a patient who weighs 100 kg?—“or 100 to 200 mg/day in slight disorders, 300 to 600 mg/day in moderate disorders or 700 to 900 mg/day in serious disorders?”, without defining the type of disturbance (kidney stones, Lesch-Nyhan syndrome, gout, tumour lysis syndrome, etc.) or the seriousness (is gout a serious illness compared to Lesch-Nyhan syndrome or tumour lysis syndrome?)

As misinformation is plentiful, we recommend patients with renal failure should start treatment with a dose of 100 mg/day (curiously, the maximum recommended dose in the same technical file in the case of a patient with severe kidney failure). What stands out is that “dosage terms should not be based on creatinine clearance due to the imprecision of low clearance values,”<sup>15</sup> when the estimations with MDRD or Cockcroft are more precise in patients with renal failure than with those with normal renal function and are usually used in daily clinical practice to correct the drug doses prescribed for patients with renal failure. For our comfort, we recommended that “if there are facilities, the plasma concentrations of oxypurinol should be controlled, and the dose should be adjusted to maintain the plasma concentrations of oxypurinol below 100 µmol/l (15.5 microgram/ml).<sup>15</sup> If anyone has these facilities in clinical practice, congratulations.

## Future

From the epidemiological point of view, this is about ascertaining if gout itself or if different variables (amount of deposit, clinical seriousness, sub-clinic inflammation, etc.) are associated with greater vascular risk. If this risk can be modified through early diagnosis and treatment of uricemia and inflammation, this will establish a *before* and an *after* in considering gout as a “respectable” disease entity for Rheumatology. Studies on the impact of correct implementation of therapeutic measures in health-related quality of life (HRQoL) will likewise allow us to see that treating and properly following up patients with gout is perceived as beneficial by the patient.

Likewise, we should assess the action impact on epidemiological variables associated to gout development on gout patient treatment and whose implementation is insisted on the basis that they are associated with a statistical risk of developing gout, not from intervention studies that support efficacy—efficiency would be even more difficult—of these measures in patients with gout. The “tolerance” of long-term patients for certain actions that are highly restrictive does not seem to be high *a priori*, and it would be desirable to have clinical data that showed the real benefit for patients of restrictions that go further than those reasonably recommended as general health measures.

The development of monoclonal antibodies against IL-1 will allow chronic inflammation to be blocked in patients with serious gout and persistent chronic inflammation or with continuous acute inflammation episodes. Patients with a high vascular risk are in my opinion ideal candidates to try out these drugs to see if chronic inflammation induced by crystals means an extra vascular risk on which to intervene.

New uricemia-reducing drugs (febuxostat, pegloticase), together with new drugs that are being developed (whether enzyme inhibitors or uricosuric agents) with in progress trials on both monotherapy and, very interestingly, therapy with a combination of allopurinol and febuxostat, will provide alternative therapies for patients having insufficient uricemia control.

The oldest drugs for acute gout treatment and hyperuricemia deserve more research to optimise their handling with data

proceeding from trials and cohorts that allow the assessment of their efficacy and safety in situations that can be extrapolated to clinical practice. Obviously, this type of research is probably destined to be independent and requires the implication of the Public Administration, health institutions, scientific societies and mainly rheumatology clinics not only for their design but for them to be carried out. The positive attitude for independent research by the Public Administration at a recent meeting with the Ministry of Health is a first step.

Developing practical clinic guidelines will allow an optimisation on how to handle gout, as the recommended publications in Europe, although an excellent starting point, suffer from uncertainty regarding specific clinical handling. This is without doubt due to the variety in availability, indication, dosage and (why not) usual clinical practice of the different drugs in the different European Union countries that experts face when issuing these recommendations.

New imaging techniques, such as high resolution ultrasound with colour Doppler, high resolution MRI and dual energy CT, will selectively allow assessment and monitoring of the spread, severity, joint inflammation and response to treatment of the selected cases.

In conclusion, gout is a disease with a great history, an interesting although complex present and a promising future that depends, to a great extent, on our respect, interest and dedication.

#### Conflict of interest

Consultant for Menarini y Ardea. Lecturer for Menarini y Ardea.

#### Acknowledgements

This article has been partially financed by a research scholarship from the Rheumatology Association of the Hospital de Cruces.

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