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The role of urate and xanthine oxidase in vascular oxidative stress: future directions

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Abstract: Vascular oxidative stress has been shown to be a potent factor in the pathophysiology of endothelial dysfunction. Despite current optimal evidence-based therapy, mortality from various cardiovascular disorders remains high. The search for newer, novel ways of attenuating endothelial dysfunction has yielded several new and exciting possibilities, one of which is the manipulation of urate levels using xanthine oxidase inhibitors. Agents such as allopurinol have shown marked improvements in vascular endothelial function in various cohorts at risk of cardiovascular events. Most of the evidence so far comes from smaller mechanistic studies. The few large randomized controlled trials have failed to show any significant mortality benefit using these agents. This article highlights the potential avenues of further research such as dose-response, and the potential for these agents to regress left ventricular hypertrophy. The role of newer agents such as febuxostat and oxypurinol are discussed as well as potential reasons why some of the current newer agents have failed to live up to the promising early-phase data. It is crucial that these remaining questions surrounding urate, xanthine oxidase and the role of various agents that affect this important oxidative stress-generating system are answered, and therefore these promising agents should not be discarded prematurely.

Keywords: urate, allopurinol, vascular oxidative stress, febuxostat

Introduction

The adverse effects of oxidative stress on the vascular endothelium have been extensively studied in the past.¹⁻⁵ The major reactive oxygen species (ROS) producing enzyme systems are the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase and xanthine oxidase (XO) systems. The most potent inducer of NADPH oxidase is angiotensin II.^{6,7} The use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are widespread in medicine for hypertension, post-myocardial infarction remodeling, proteinuria as well as heart failure. Much less attention has been paid to the XO system despite the availability of new and established XO inhibitors such as oxypurinol, febuxostat and allopurinol. The mechanism by which XO catalyzes hypoxanthine and xanthine conversion is extremely complex and have been previously described in detail.^{8,9} A fully reduced XO contains 6 electrons and its re-oxidation involves electron transfer to oxygen molecules which generates 2 hydrogen peroxide (H_2O_2) and 2 superoxide anion (O_2^-) species⁹ for every fully reduced XO molecule. There have been many studies looking at the role of urate and urate-lowering agents on endothelial function.¹⁰⁻¹⁶ Our group have shown in the past that the improvement in endothelial function seen with allopurinol is due to its ability to inhibit xanthine oxidase, and therefore ROS that are produced as a by-product of urate formation. Urate,

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therefore, is likely to be a marker of XO activity rather than a culprit per se.¹⁰ Although there are exciting prospects for the improvement of endothelial dysfunction using XO inhibitors in high risk cohorts, most of these have come from small mechanistic studies.

The question that needs to be addressed now is: how do we proceed from here in this area of research so that the full therapeutic potential of XO inhibitors can be realized? There is clearly some mileage in these agents that needs to be exploited further and these agents should not be prematurely discarded. This article hopes to stimulate discussion and highlight several new possibilities for further study that could potentially clarify some of the unresolved issues about the roles that allopurinol, urate and XO play in vascular biology.

Further dose-ranging studies

The importance of dose-response studies cannot be underestimated. This is true even for established treatments such as ACE inhibitors and ARBs. For example, through unusual means of studies in patients who have taken overdoses of ACE inhibitors, it has been discovered that much more blood pressure lowering can be achieved by the use of doses higher than in normal clinical use.¹⁷ At the same time other groups have shown that ultra-high doses of ARBs, which also act on the renin-angiotensin system, have very little additional blood pressure lowering over standard doses but may exert other beneficial effects on target organs.¹⁸

Our mechanistic dose-response studies¹⁰ were the first to demonstrate that high-dose allopurinol (600 mg/day) reduces vascular oxidative stress in congestive heart failure (CHF) significantly more than conventional doses (300 mg/day). The question remains whether or not even higher doses would provide a further improvement on endothelial function. A careful study into methods employed by various trials using allopurinol in early pharmacokinetic data^{19,20} and *in vivo* studies measuring XO²¹ reveals that the oxypurinol concentration achieved by 600 mg of allopurinol is 9.56 mg/L.¹⁹ Taking into account the molecular weight of allopurinol (136 g/mol), this equates to a concentration of 0.07 mmol/L. Preliminary experiments by Spiekermann et al,²¹ have shown that plasma XO activity *in vivo* is completely inhibited by an oxypurinol concentration of 0.1 mmol/L. Interestingly, there has also been pharmacokinetic data on 900 mg/day allopurinol which achieves *in vivo* concentrations of 0.09 mmol/L.¹⁹ This means that 900 mg of allopurinol could almost completely inhibit XO activity. How this inhibition will affect overall purine metabolism is not yet clear. These initial studies were done in fit, healthy males aged 21 to 26 years of age with normal

renal function. It nevertheless shows that there is further potential for oxidative stress reduction at even higher doses. Elderly patients, on the other hand, tend to demonstrate higher oxypurinol concentrations possibly due to reduced renal clearance of oxypurinol and a diminished volume of distribution but a lower level of XO inhibition per dose of allopurinol²⁰ therefore making them more susceptible to side effects. However, further careful dose-ranging studies up to 900 mg/day of allopurinol could be informative.

Left ventricular hypertrophy (LVH) regression

Chronic treatment with allopurinol has been shown to prevent adverse LV remodeling, decrease LV weight and reduce LV collagen density in animal models with heart failure.²² It is well known from Framingham²³ and from a meta-analysis of 48,545 individuals by Vakili et al²⁴ that LVH independently confers high cardiac risk, irrespective of blood pressure. After age, LVH is said to be the strongest independent predictor of cardiovascular (CV) events, CV deaths and total mortality.²⁵ LVH is thought to be a culprit for 4 reasons: it is intrinsically arrhythmogenic, reduces coronary perfusion reserve,²⁶ and it causes diastolic heart failure and left atrial dilatation leading to atrial fibrillation (AF) and embolic strokes.

Despite a “normal” blood pressure, LVH confers the same extra risk in normotensives as it does in hypertensives.²⁷ Nevertheless, we know that regressing LVH irrespective of blood pressure changes is an effective way to reduce risk.^{28,29} Furthermore, in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study, LVH regression reduced CV events/mortality independent of blood pressure. In LIFE, losartan reduced both LVH and CV events more than atenolol despite their both reducing blood pressure equally. LVH regression reduced incidence of new-AF, new onset diabetes, HF hospitalization, sudden deaths and strokes.³⁰⁻³²

Since controlling BP and using an ACE inhibitor is only partially effective at regressing LVH, we now need additional ways of regressing LVH. Apart from controlling the BP, the other main therapeutic target that we know about and whose manipulation should regress LVH is oxidative stress. There is now clear evidence that oxidative stress triggers cardiomyocyte hypertrophy.^{33,34} If oxidative stress mediates LVH, then reducing oxidative stress should be a promising novel approach to preventing or regressing LVH.

Since oxidative stress is a key culprit producing LVH, it seems sensible to explore therapies which reduce oxidative

stress (other than ACE inhibitors) to see if they also reduce LVH. We found allopurinol to be exceptionally potent against ROS in that it can abolish endogenous oxidative stress in blood vessels that would otherwise be sensitive to supra-physiological doses of vitamin C, a well recognized scavenger of reactive oxygen species.^{10,35} Therefore allopurinol becomes a prime therapeutic option to see if it can regress LVH.

Other therapies which prevent oxidative stress forming (like ACE inhibitors) have already been very successful in general and in particular ACE inhibitors are known to regress LVH. Since allopurinol dramatically improves oxidative stress and its consequence, endothelial dysfunction and since oxidative stress is a major mediator of LVH, it seems sensible to explore whether allopurinol will also regress LVH. We are currently exploring this possibility in optimally treated patients with LVH using magnetic resonance imaging.

We have also found that allopurinol significantly reduces augmentation index ($27.6 \pm 3.4\%$ to $20.1 \pm 2.2\%$ $P < 0.05$) which implies reduced LV afterload.¹¹ Falls in augmentation index have been shown to be the best predictor of falls in LV mass because augmentation index correlates with LV afterload.³⁶ The idea that allopurinol reduces LV afterload is confirmed also by the fact that allopurinol reduces B-type natriuretic peptide which is a measure of intracardiac pressure.³⁷ We are currently investigating the effects of allopurinol on LVH and arterial stiffness using indices of vascular stiffness and cardiac magnetic resonance.

Febuxostat

Although allopurinol is a very efficiently absorbed drug, it is a relatively weak inhibitor of XO with IC_{50} concentrations of between 0.2 and 50 μM .³⁸ Febuxostat [2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid] is a new non-purine XO inhibitor, which has a higher bioavailability and a more potent XO inhibitory effect than allopurinol.³⁸ It would therefore theoretically be more effective than allopurinol in lowering urate. It also has the advantage of being metabolized mainly by glucuronide formation and oxidation in the liver³⁹ which would make it a better choice of XO inhibitor than patients with renal disease. It is currently licensed by both the US Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) for use in chronic hyperuricemia. However, in clinical trials, it did not reduce the frequency of attacks of gout,³⁹ it is not as well tolerated as allopurinol⁴⁰ and it possibly increased mortality compared to allopurinol.⁴¹ Once again, a dose ranging study of similar design will be able to identify a dose of febuxostat

at which oxidative stress is effectively inhibited using this newer agent. Comparisons between febuxostat and allopurinol can then be made for a similar degree of urate lowering. This agent is potentially a more powerful antioxidant than allopurinol given its pharmacokinetic interactions with XO and therefore could be studied more closely to ascertain the full range of its potential therapeutic benefits.

Oxypurinol

The most high profile XO inhibitor of late has been oxypurinol. Oxypurinol, also known as alloxanthine, is the active metabolite of allopurinol. It is licensed for the treatment of chronic hyperuricemia by the FDA. Unfortunately, oxypurinol research, particularly since the OPT-CHF trial,⁴² has almost ground to a halt. The OPT-CHF trial was a randomized controlled trial of oxypurinol 600 mg/day versus placebo in 405 patients with NYHA Class III and IV heart failure on optimal medical therapy. Allopurinol is theoretically less potent than oxypurinol because during its conversion to oxypurinol, it serves as a substrate for oxygen reduction to O_2^- . This makes it an initial source of O_2^- generation.^{43,44} Allopurinol inhibition of O_2^- production from XO requires both its oxidation to oxypurinol and stabilization of the oxypurinol-XO complex.⁴⁵ *In vitro* studies also suggest that oxypurinol is a more potent OH^- scavenger⁴⁶ and improves mechanoenergetic coupling in animal heart failure models.⁴⁷ Although two recent high profile studies, EXOTIC-HF and LA PLATA using oxypurinol, have demonstrated a significant improvement in left ventricular ejection fraction (3.3% and 3.6% respectively) in the acute setting, the subsequent OPT-CHF trial also using oxypurinol chronically for a 6-month duration failed to produce significant clinical improvements in unselected patients.^{48,49} There are many reasons that one could speculate on the reasons of the OPT-CHF trial outcome such as the efficacy of the oxypurinol dose used⁵⁰ but the researchers must be given credit for taking on this area and attempting to answer an important question in a high risk cohort to which a clear answer does not exist to this day.

However, OPT-CHF was a small study looking at an efficacy endpoint which was a composite that incorporated measures of patient outcome and well-being. It was not powered for a mortality analysis. A subsequent retrospective analysis suggests that a subgroup of patients with high baseline urate (>0.57 mmol/L) might benefit.⁴⁹ In theory, oxypurinol should be preferable to allopurinol in inhibiting XO as the metabolism of allopurinol into oxypurinol itself generates O_2^- .⁴³ Data from the oxypurinol bioequivalence

AAI-US-175 study showed that 600 mg oxypurinol had a relative bioavailability equivalent to only 81 mg allopurinol.⁵¹ Therefore it is possible that patients on OPT-CHF were underdosed for an effect to be seen as most studies showing benefit of allopurinol have used at least 300 mg/day.

Heparin interaction

XO is bound to the surface of endothelial cells by glycosaminoglycans and is released following displacement by bolus injections of heparin. Relatively low doses (50 iu/kg body weight) result in a threefold rise of XO levels in healthy volunteers.⁵² This is the basis of various *in vivo* experiments looking at levels of XO expression. The clinical implications of this could be enormous as heparin is widely used in patients with acute cardiovascular complications. Does this mean that patients with an acute coronary syndrome who are being treated with heparin require concomitant treatment with a XO inhibitor like allopurinol to reduce the burden of oxidative stress? Do low-molecular-weight heparins have the same effect of XO displacement from glycosaminoglycans as unfractionated heparin? It would be fascinating to now do studies exploring these issues which could potentially be of major clinical importance. Therefore, a double-blind, placebo-controlled study of allopurinol in acute coronary syndrome patients treated with heparin is needed.

Conclusion

These potential routes forward represent an exciting challenge for researchers in vascular biology. They will help further clarify the possible role of allopurinol or other agents discussed in this article in managing patients who remain at risk despite current evidence-based treatments.

Disclosures

The authors disclose no conflicts of interest.

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