Update on the Management of Hyperuricemia and Gout

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Abstract
Gout is the most common inflammatory arthritis in the United States, with more than three million sufferers. Management of gout has changed relatively little in the past 50 years, despite the fact that many gout patients have contraindications to one or more currently available gout therapies. However, recent insights into gout pathophysiology suggest that time is ripe for a change. This article reviews recent updates in the management of gout, including new insights into dietary management that may permit better control of hyperuricemia. Also reviewed are the biological and clinical data behind newly-developed drugs for gout that are likely to receive serious consideration for FDA approval, and clinical use, in the foreseeable future.

Gout is the most common inflammatory arthritis, with more than three million sufferers in the U.S. alone. The majority of cases of gout are managed by primary care physicians, with referral to rheumatologists typically for more difficult cases. However, recent studies indicate that primary care management does not always adhere to evidenced-based best practice. Moreover, even in the hands of experienced rheumatologists, a significant number of patients fail to achieve optimal response to appropriate therapy. In contrast to the view of gout as a relatively benign disease, poorly managed gout can be disabling and lead to joint destruction, joint infection, and, occasionally, amputation and death. Moreover, accumulating evidence suggests that gout and hyperuricemia are associated with, and potentially contributory to, a number of serious and potentially life-threatening problems, including hypertension, renal disease, and coronary artery disease. Accordingly, more and better treatment options are needed for patients with gout and hyperuricemia. Included in this article are reviews of the most recent data on the potential importance of lifestyle modification in the management of hyperuricemia and gout and new information regarding the appropriate use of currently available standard therapies for gout. A discussion follows on agents that are newly available, nearly available, and potentially available in the future for the management of hyperuricemia.

Food and Drink: Lifestyle Modifications and the Management of Gout

Surf ‘N Turf
Clinicians have known, for more than a millennium, that dietary indiscretions may predispose to the risk of gouty attack. Decreases in the consumption of meats (especially organ meats), and other foods with high purine content (such as seafood), have long been advised by clinicians. Given this well-established standard of practice, readers may be surprised to know that, while many small studies have established the role of diet in hyperuricemia and gout, few studies that were rigorous, large scale, or both, have confirmed these initial observations. To address this deficiency, Choi and colleagues utilized the Third National Health and Nutrition Survey (NHANES III), a database containing information on approximately 15,000 patients. At entry into this study, patients completed extensive questionnaires on their nutritional status, including information on diet and alcohol intake, as well as general health information. Patients then underwent a detailed physical examination, as well as a
laboratory testing, including serum uric acid determination. For the purposes of the study, the investigators divided the patients into five quintiles based on daily consumption of each of the foods of interest. In so doing, they confirmed that patients with higher intakes of either meat or seafood had increased risks of hyperuricemia. However, several observations were also made that were less expected. Based on the risk of hyperuricemia with meat and seafood intake, practitioners sometimes assume that protein per se carries an increased risk of hyperuricemia. This study found that, once corrected for purine intake, there was no correlation between dietary protein intake and uric acid levels. Thus, the increased risk for elevated serum uric acid concentration when eating meat or seafood appears to reside, primarily if not exclusively, in the purine content of these foods.

Got Milk?
Choi and coworkers also examined whether consumption of dairy products was associated with changes in serum uric acid concentration. A number of small observational and provocation studies, or either, performed over the past decade have suggested that dairy intake may independently contribute to lower uric acid levels. NHANES III supports these observations. In the studies by Choi and associates, patients with the highest intake of dairy products had average serum uric acid levels nearly 0.5 mg/dl lower than patients with the lowest levels of intake.5

How might dairy consumption actively contribute to lower uric acid levels? Several additional small studies suggest the possibility that milk or milk components may have a uricosuric effect. For example, Garrel and colleagues tested the effect of two isolated milk proteins, casein and lactalbumin, using soy protein as a control, on 10 healthy volunteers between the ages of 20 and 30 years.6 Each participant consumed 80 grams of casein, lactalbumin, or soy protein, followed by measurement of serum and urinary urate levels for the next 180 minutes. Volunteers consuming the casein or lactalbumin experienced rapid decreases in serum urate levels. In contrast, consumption of soy protein resulted in a rapid increase in serum urate levels. When the investigators assessed the urine urate levels, they observed that ingestion of any of the three proteins tested resulted in increased urinary urate excretion. Based on these observations, they suggest that, rather than contributing to hyperuricemia, ingested protein per se has a direct uricosuric effect, to which the effects of the dairy proteins (and presumably dairy products themselves) can be ascribed. What is notable about dairy products, however, is that they are extremely low in purines; in contrast, the soy protein control used in the study was actually high in purine impurities. Thus, the investigators propose that it is the unique high protein and low purine nature of dairy products that contributes to their urate lowering effects. Support for the uricosuric effects of proteins can be found in several physiologic studies.7 Although the mechanism for protein-mediated urate excretion had not been determined, at least one investigator has suggested that it may be the action of amino acids rather than intact protein, competing as weak acids at renal urate transporters, that acts to block urate uptake and induce uricosuria. Whether dairy intake could have a urate-lowering action in patients with significant renal insufficiency has not been tested, but would seem to be unlikely under the current model.

The above studies link meat and seafood, but not protein or dairy, to high serum urate levels. But do these observations translate to a risk for the development of actual gouty attacks? To assess this question, Choi and coworkers turned to the Health Professionals Follow-up Study, in which more than 50,000 dentists, podiatrists, and other health care professionals participated.8 In this study, male patients were enrolled and followed prospectively for 12 years. Dietary information and other medical history were collected at the time of enrollment. After excluding participants with preexisting gout or renal disease, they followed the remaining patients, identifying by self-report approximately 700 patients who developed new onset of gout during the study period. Consistent with the NHANES III data for hyperuricemia, patients in the upper quintiles of meat or seafood consumption were at significantly more risk for gout than patients in the lower quintiles were at risk. In contrast, patients in the highest quintiles for dairy consumption were at significantly lower risk for new onset of gout than individuals in the lowest quintiles. Thus, although no prospective trials have yet examined the benefit of increased dietary dairy in lowering the risk of gouty attacks, these data suggest that increasing dairy intake may be both an easy and effective way to improve the management of gout.

Nutritionists have long known that some green vegetables, particularly leafy vegetables, such as spinach, are high in purines, and have consequently recommended that patients with gout reduce their consumption of these vegetables. However, Choi and associates found no correlation between vegetable intake and gout risk. It is proposed that other, beneficial compounds present in these vegetables, perhaps with the capacity to induce renal urate excretion, might offset the adverse consequences of their high purine content. Further study will be required to understand the nature of these effects.

Beer Me, Marge: Alcohol and Hyperuricemia
Ancient Greek and Roman physicians were well aware of the capacity of alcoholic beverages to predispose one to gout, an observation that was also not lost on the great European physicians of the 15th through 19th Centuries. It has been presumed that all alcoholic beverages, including beer, wine, and hard liquors, carry increased risks for hyperuricemia. Alcohol consumption has multiple mechanisms by which it can raise serum urate, including the generation and turnover of ATP (adenosine triphosphate), diuresis and dehydration, the production of lactic and ketoacids, and the content of
purines in some alcoholic beverages.

As in the case of food, however, the effects of alcohol have been documented in many small, but few large or definitive studies. To address this deficiency, Choi and coworkers again employed the NHANES III and Health Professionals databases. Using these data, these investigators confirmed a nearly linear dose response between alcohol ingestion and both serum urate and the risk of gout. When alcohol consumption was further broken down by type of beverage, however, an unexpected observation arose. Beer ingestion was most strongly correlated with hyperuricemia and gout (presumably because of the very high content of purines in beer and ale), hard liquor consumption increased serum urate and risk of gout to an intermediate degree, but moderate consumption of wine had little or no effect on either serum urate levels or the risk of gout. How could this be? The answer remains uncertain, but wine in general is a more complex ferment than either beer or hard liquor; wines contain a number of antioxidants including polyphenols. Resveratrol, an antioxidant that in animal models has been shown to have life-extending properties, is also found in wine but not other alcoholic beverages. Moreover, wine contains less alcohol per volume than either beer or liquor, suggesting a lower ratio of alcohol to other bioactive compounds. It is therefore possible that wine induces complex effects, either abrogating or offsetting the alcohol-based production of purines as a result of its other ingredients. In this regard, it is interesting to consider whether red wine, which has a more complex structure (and is the only type of wine containing significant quantities of resveratrol), might engender more anti-hyperuricemic properties than white. Studies addressing the relative effects of red and white wine have yet to be performed, however.

The Pepsi Generation: Fructose Intake and the Risk of Hyperuricemia and Gout

Osler suggested, more than one hundred years ago, that sugar intake might contribute to the risk of gout. Recent events and recent studies are beginning to bear him out. The prevalence of gout has undergone a striking increase in the last 50 years, concomitantly with increases in obesity and diabetes. Indeed, studies suggest a three- to four-fold increase in the frequency of gout in the U.S. during this period. To understand a possible reason for this sea change, one must consider the consumption of sugar. Until approximately the 17th Century, the primary source of sweetener in the western diet was honey. Around that time—and concordant with the trade routes and slave trade in the West Indies—cane sugar, or sucrose—came into use, initially as a luxury only for the upper classes. By the late 18th Century, the primary source of sweetener in the western diet was honey. Around that time—and concordant with the trade routes and slave trade in the West Indies—cane sugar, or sucrose—came into use, initially as a luxury only for the upper classes. Indeed, recent studies indicate that the average American currently consumes more than 160 pounds of sugar annually and that the single biggest source of calories in the American diet (11%) is now soft drinks and fruit juices. Critically, it turns out that the metabolism of fructose is unique, and that the metabolic degradation of fructose generates uric acid to a degree greater than that seen with other sugars. Indeed, both human and animal studies have demonstrated that ingestion of fructose rapidly leads to increases in serum urate. Strikingly, the increases in gout incidence and prevalence in the U.S. began to take off around the 1960s just as fructose consumption began to skyrocket.

To understand how fructose may induce hyperuricemia, we must briefly review the pathway of purine and uric acid biosynthesis (Fig. 1). Purines are synthesized off a backbone of 5-ribose pyrophosphate by the action of phosphoribosyl pyrophosphate (PRPP) synthase, resulting in the production of inosine monophosphate. However, inosine monophosphate can also be generated by the action of AMP deaminase on AMP. Inosine monophosphate may then be converted to inosine by 5’ nucleotidase, which, in turn, is converted to hypoxanthine by the action of nucleoside phosphorylase. Hypoxanthine then serves as the substrate for xanthine and subsequent uric acid synthesis by xanthine oxidase. Under normal circumstances, several feedback loops act to reduce the production of uric acid, including inhibition of AMP deaminase by inorganic phosphate, and inhibition of 5’ nucleotidase by elevated concentrations of ATP.

When fructose is ingested, it is acted upon by the enzyme fructokinase to produce fructose-1-phosphate, consuming in...
the process one molecule of ATP and generating ADP and inorganic phosphate (P). This enzymatic action is essentially irreversible, since fructose-1-phosphate acts as a phosphate sink, leading to Pi sequestration. As a result, instead of being regenerated to ATP, the ADP produced during fructose metabolism is susceptible to conversion to AMP by adenylate kinase; AMP is then available to participate as a substrate for uric acid generation. Moreover, the depletion of both ATP and Pi during fructose metabolism diminishes the activity of the feedback inhibitory loops, permitting the enzymatic processes involved in uric acid generation to accelerate.

In addition to these observations, Vitart and associates have recently identified a novel renal urate transporter, SLC2A9, whose genetic variants appear to influence serum urate concentrations. Since SLC2A9 has also recently been established as a fructose transporter, these data suggest that fructose may also alter serum urate through its effects on the modulation of urate transport.

Do these biochemical effects of fructose ingestion actually result in human hyperuricemia? Small prospective studies have indicated the ability of diets high in fructose to increase higher serum urate levels relative to diets high in glucose or low in carbohydrates. To address this question on a larger scale, Choi and colleagues again examined their databases. They observed a direct correlation between the degree of fructose intake overall, or measured as soft drink consumption, and the risk of both hyperuricemia and gout. Males appeared to be more susceptible to the fructose effect than females. Moreover, for individuals who consume diet soda, no correlation was seen between the amount of drink consumption, and the risk in hyperuricemia or gout, confirming that it is likely to be the fructose in soft drinks that is the main offender.

Strange Brew: Coffee Consumption and the Mitigation of Hyperuricemia

Caffeinated beverages, such as coffee and tea, are drunk worldwide, and coffee is perhaps the most popular beverage on the planet. By acting on various subtypes of adenosine receptors, caffeine stimulates wakefulness and may have other potential actions, including the abrogation of hepatic fibrosis and mixed pro- and anti-inflammatory effects. Since caffeine is also a diuretic, and diuretics tend to increase the risk of hyperuricemia and gout (by stimulating proximal tubular sodium resorption, and by directly affecting urate excretion), one might postulate that drinking caffeinated beverages could contribute to hyperuricemia. Such was the reasoning of KiyoHara and coworkers when they tested the effects of coffee and tea on uric acid. To do so, they surveyed 2240 Japanese Defense Officials receiving a pre-retirement physical. Dietary information was obtained and compared with the participants’ serum urate levels. However, the investigators failed to observe a direct correlation between coffee consumption and hyperuricemia. On the contrary, their study showed a clear inverse correlation between these two variables, suggesting the possibility that caffeine, or some other component of coffee, might actually contribute to a reduction in serum urate levels. In fact, these investigators concluded that it was unlikely that the active compound was caffeine, since increases in the consumption of coffee-containing green tea carried no similar association with hyperuricemia.

Choi and associates reexamined the effects of caffeine using the NHANES III database and observed that heavy coffee drinking (four or more cups) was associated with significant decrements in serum urate levels. Once again, it appeared unlikely that caffeine was the effector, since increased consumption of tea had no effect. Moreover, consumption of decaffeinated coffee was also associated with lower serum urate levels. Thus, it appears likely that a coffee component(s) other than caffeine must play a role in lowering uric acid. What this component may be, and its mechanism of action, remain a mystery; but it is worth noting that coffee is actually a complex beverage and contains a wide range of organic plant alkaloids.

Novel Therapeutics and New Horizons

The currently available drugs for gout, NSAIDS (nonsteroidal antiinflammatory drugs), glucocorticoids, colchicine, and the urate-lowering therapies (allopurinol and probenecid) are all well established and reasonably effective. However, there are a number of good reasons to desire the availability of new and different therapies. Rheumatologists are aware that some patients fail to respond to the most aggressive of current regimens. These are individuals who, despite maximum therapy, continue to have high serum urate levels, tophi, or frequent gouty attacks, some a combination. Moreover, our current urate-lowering therapies are only moderately effective at reducing or resolving tophi, with probenecid carrying the additional potential risk of inducing renal stones when used in the setting of a large total body urate burden. Additionally, many patients with gout have significant and often multiple comorbidities that make the use of many of our current therapies undesirable or, in some cases, absolutely contraindicated.

To understand the extent to which our current gout drugs may be contraindicated in the patient population, we recently conducted a spot survey in an active department of a Veterans Affairs rheumatology clinic, which has a high gout case load. We defined five potential contraindications to currently available gout therapies: 1. chronic kidney disease (CKD, serum creatinine greater than 1.6 mg/dl in patients over the age of 50), 2. diabetes, 3. hypertension, 4. coronary artery disease, and 5. allopurinol sensitivity (all by previous chart diagnosis or current history). We then asked what percentage of gout patients presented with what condition(s). The presence of these comorbid conditions in our gout patients was extremely high, perhaps as a consequence of the current epidemic of Syndrome X. When we subsequently defined hypertension, CKD, diabetes, and coronary artery disease as relative
contraindications for both NSAIDs and glucocorticoids, and CKD as a contraindication for colchicine or probenecid, we observed that a very high proportion of our patients (90%) had contraindications to at least one currently available gout drug. Worse, we observed that a significant proportion of our patients had contraindications to all, or most of the drugs available (Fig. 2). These observations have been borne out in other studies, and suggest the need for more effective, safer, and better-tolerated therapies for gout.

**Pipeline Therapies**

**Febuxostat**

For the past several years, rheumatologists have been watching with interest the development of an alternative to allopurinol. That development is now coming to fruition, with the recent approval of febuxostat by the European Commission, the European equivalent of the U.S. Food and Drug Administration. Like allopurinol, febuxostat acts by inhibiting the enzyme xanthine oxidase, responsible for the conversion of hypoxanthine to xanthine and then uric acid. Similar to allopurinol, febuxostat is administered once daily, by mouth. However, febuxostat differs from allopurinol in several potentially important aspects. In contrast to allopurinol, which is itself a purine structure, febuxostat is not a purine analog, but rather a mixed inhibitor of xanthine oxidase. It is possible that this chemically different structure may render febuxostat safe in patients with allopurinol hypersensitivity. If this turns out to be the case, failure to cross-react with allopurinol would be extremely useful for physicians managing gout patients with allopurinol hypersensitivity. Unlike allopurinol, febuxostat is also not susceptible to degradation by purine pathway enzymes, giving a longer half-life and potentially a more kinetically consistent action. Also of interest is the fact that febuxostat is much more selective than allopurinol. Whereas allopurinol inhibits both xanthine oxidase, and to a lesser extent several other enzymes in the purine biosynthetic pathway, febuxostat appears to inhibit xanthine oxidase exclusively. Whether and in what ways this increased selectivity turns out to be advantageous remains to be determined. On a molar basis, febuxostat is also more a potent xanthine oxidase inhibitor than allopurinol, with a lower IC₅₀ demonstrated in vitro. Again, the benefit of this difference remains to be determined, but suggests the possibility that febuxostat might permit clinicians to more readily reach target serum urates within the range of safe use of the drug. Finally, febuxostat is not renally excreted, suggesting its possible utility in patients with CKD. In this regard, however, it must be noted that Phase III studies of the utility of febuxostat in patients with CKD have yet to be reported; and again, rheumatologists are generally aware that allopurinol doses can be escalated, albeit cautiously, in renal failure patients. One area in which febuxostat and allopurinol are similar is that they are both heptically metabolized; it remains unclear the extent to which preexisting liver disease is a contraindication to febuxostat use, but caution will certainly be warranted, and in some patients, febuxostat use has been associated with increases in serum liver enzyme levels.

Febuxostat has been tested in Phase I, Phase II, and Phase III trials. Based on dose-finding studies, approval of febuxostat in Europe will be limited to once-daily 80 and 120 mg doses, and these are the doses at which the Phase II study was carried out. Taking as the primary endpoint a lowering of serum urate to below 6.0 mg/dL, febuxostat 80 mg and 120 mg were each more effective at achieving the target urate level than allopurinol 300 mg. Once again, it must be affirmed that rheumatologists do not treat gout with a fixed dose of allopurinol, but rather titrate to the target serum urate level. Accordingly, the statement that febuxostat 80 or 120 is more effective than allopurinol 300 mg provides only limited insight into the relative utility of the agents. When the secondary endpoint of gout flares was examined, both febuxostat 80 mg and 120 mg were more effective than allopurinol 300 mg at inducing early flares. Presumably, the efficacy of febuxostat, in this regard, was a consequence of its more effective urate lowering ability, since rheumatologists know well that rapid lowering of serum urate can temporarily increase the risk of acute gout attacks. (In the studies reported, colchicines or NSAID prophylaxis against acute attack was limited to the first 2 weeks of urate-lowering therapy, in contrast to the longer prophylaxis that is standard-of-care in the community). Later (3 to 12 months), the urate lowering capacity of the two drugs appeared similar, with febuxostat demonstrating a somewhat greater efficacy. The clinical significance of these differences remains uncertain.

**Pegylated Uricase**

Humans, along with their primate cousins and New World monkeys, experienced the mutational loss of the enzyme uricase in the Miocene era, approximately 20 million years ago. It would not be until the mid-twentieth Century, however, that humans were able to consider the possibil-

![Figure 2](https://example.com/figure2.png)

Figure 2 Prevalence of contraindications to specific gout drugs among a clinic population. Gout patients presenting to a rheumatology clinic over 4 consecutive weeks were assessed for contraindication to five separate gout agents, and the percentage affected was calculated, as described in the text.
ity of exogenous uricase replacement. More recently, technological advances have permitted the production of recombinant bacterial uricase (rasburicase), derived from aspergillus and approved for use in preventing tumor lysis syndrome. It was not long before rasburicase was being explored, in a small number of refractory patients, for the treatment of gout. In some cases, rasburicase was able to lower uric acid where other treatments had failed. Indeed, the ability of rasburicase to dramatically lower serum urate levels has led, in some instances, to an impressive resolution of tophi. Rasburicase is not generally suitable for chronic use, however. For one thing, it is expensive: approximately $8,000 a dose. As a foreign protein, rasburicase has a very short half-life in the bloodstream, requiring multiple doses to create extended effects. Moreover, as a foreign protein, rasburicase is highly immunogenic, and with each successive treatment tends to be more rapidly cleared by the immune system. The prospect of immediate hypersensitivity reactions, including anaphylaxis, has also been a limiting factor. Thus, while rasburicase is not generally suitable for extended use, it may have value as a bridge therapy in selected patients.

To overcome the limitations of fungally derived uricase, investigators decided upon a strategy beginning with the platform of a recombinant mammalian uricase, derived from pig, but modified to reflect primate sequence at the carboxy terminus. They then explored the benefits of appending to the protein chains of methoxypolyethylene glycol (PEGylation, an established strategy for making proteins more stable and less immunogenic in the blood). These researchers found that the optimal level of PEGylation was six PEG chains of 10 units each. With this agent, called peguricase, in hand, Phase I trials were performed that identified optimal dosing of the agent as 8 to 12 mg on a monthly or biweekly basis. Initial Phase I trials assessed the feasibility of subcutaneous administration; interestingly, patients receiving subcutaneous peguricase had an increased risk of antibodies, not to the protein, but to the PEG; the presence of these antibodies correlated with a shorter half-life of the agent. Subsequent switching to intravenous administration reduced the extent of this problem, possibly because intravenous administration permitted peguricase to bypass exposure to dermal dendritic cells. In these Phase I trials, the administration of peguricase was highly effective and durable in reducing serum urate levels, driving serum urate concentrations down to near zero, with gradual reaccumulation only after several weeks. Subsequently, Phase II and Phase III trials have been completed; the results have not yet been published, though some reports have been presented in abstract form. These abstracts suggest the ability of pegylated uricase to effectively lower serum urate; as in the case of febuxostat, early serum urate lowering appears to be accompanied by an increase in attacks, but subsequently (on the order of months), the number of attacks is reduced. These abstracts also suggest the ability of pegylated uricase to reduce the bulk of tophaceous deposits.

What might be the pluses and minuses of peguricase? Though much remains to be discovered, it is possible to speculate on the basis of the established properties of the agent. First, it is clear that pegylated uricase has the capacity to dramatically lower serum urate, making it attractive as a potential rescue therapy. Conceivably, patients who have failed all other agents might be referred for peguricase. The safety and efficacy of the agent in patients with renal failure has yet to be described, but there is no a priori reason why this agent should not be usable in this group of patients. Moreover, in contrast to allopurinol and febuxostat, there is no a priori reason to expect that the agent will be contraindicated in liver failure, though studies will need to be done. Again, the early studies suggest that pegylated uricase may be a good alternative therapy in patients whose total body burden of uric acid is high, and who are in need of resolution of tophaceous deposits.

Among the possible limitations and concerns regarding the use of pegylated uricase is its expense. Compared with the currently available gout therapies, all of which are generic, any biologic agent is sure to be expensive. Given the currently high prevalence of gout, its applicability to the general gout population, therefore, requires careful consideration. Another issue is the fact that, while less immunogenic than rasburicase, pegylated uricase still has the capacity to serve as an immunogen. Hypersensitivity and anaphylactoid reactions have occurred, and even when these do not occur, the ability of the immune system to recognize this agent may engender a potential loss of utility of the agent over time; future studies should clarify whether these are issues of genuine concern. Another interesting question is how low a serum urate level is actually desirable. Not only does urate have antioxidant capacity, but the action of uricase on urate generates oxygen radicals; the degree and importance of this phenomenon remains to be determined. Whether it will be useful to titrate the dose of pegylated uricase to achieve serum urates that are low, but not too low, also remains to be determined. Finally, recent studies suggest that uric acid may play a fundamental role in immune responses; whether lowering the serum urate with pegylated uricase could adversely affect the immune system is at least a theoretical question. One possible approach to balancing the efficacy, cost, and potential toxicities of peguricase may be to employ it as induction therapy, switching to more conventional agents for maintenance once significant urate depletion has been achieved.

Possible Future Approaches to Gout Management

Anti-Cytokine Therapy
The response to crystals in a joint depends upon both the ability of uric acid crystals to activate complement, and their ability to interact with and activate resident tissue macrophages. The response of tissue macrophages to crystals involves the activation of the NALP3 inflammasome, a
multimolecular complex that employs the enzyme caspase 1 to convert the pro-form of IL-1β into the active form (Fig. 3).⁴⁵,⁴⁶ Secretion of IL-1β contributes to the gouty inflammatory response in a number of ways, including stimulating the up-regulation of adhesion molecules on vascular endothelial cells. Secreted IL-1β also acts in an autacoid manner, to engage IL-1β receptors, activate the signaling molecule MyD88, and stimulate additional inflammatory reactions.⁴⁷ Given the apparent centrality of IL-1β to the initiation of gouty inflammation, So and colleagues tested the utility of anakinra, a soluble IL-1β receptor antagonist, for the treatment of acute gout.⁴⁸ Ten patients with acute gout, who either had failed or were unable to tolerate standard therapy received anakinra daily for 3 days. All ten patients experienced 50% to 100% improvement in their signs and symptoms, measured by an unvalidated gouty response score. Most patients demonstrated response within 24 hours of treatment. Considering that anakinra is already available for the treatment of other rheumatic syndromes, these studies suggest that it may be a viable treatment option for at least some patients with acute gout. Although biologic agents are expensive, the use of anakinra for only a few days would be unlikely to present a major economic burden. Whether it would also be cost effective as maintenance therapy would be a different matter.

**ACTH and Melanocortin Receptors: Old Becomes New Again**

ACTH (adrenocorticotrophic hormone) was the first steroid pathway agent used in rheumatic disease. Although its use in gout has largely been supplanted by prednisone, and though its availability in depot form is currently limited, ACTH is an effective treatment for acute gout,⁴⁹ and older rheumatologists speak anecdotally of its superior efficacy. First described by Hench and Kendall, the antiinflammatory mechanism of ACTH action has long been presumed to be due to its ability to stimulate the adrenal production of corticosterone.⁵⁰ However, ACTH is also a precursor molecule for melanocortin and is known to have activity at melanocortin receptors (MCR).⁵¹ Based on these observations, Getting and coworkers have examined the possibility that ACTH may act to inhibit inflammation via engagement of one or more MCR. Using a rat model of acute gout, they confirmed the ability of ACTH, injected subcutaneously, to stimulate increases in plasma corticosterone levels, as well as to reduce signs of inflammation such as neutrophil influx. However, they also demonstrated the ability of lower concentrations of ACTH, injected directly into the joint to inhibit joint inflammation without increasing corticosterone levels.⁵² Thus, ACTH must have antiinflammatory properties independent of its effect on glucocorticoid release. Further studies by Getting and associates have demonstrated the ability of MCR antagonists to reverse the antiinflammatory effect of ACTH and the ability of selective agonists of MCR—particularly MCR3—to suppress gouty inflammation.⁵²-⁵⁴ These data suggest that MCR3 agonists may be useful antiinflammatory drugs. Whether such agents will prove useful in human gout has yet to be tested.

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