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INSULIN DETEMIR: A NEW TOOL TO FIGHT DIABETES MELLITUS

Anthony Menezes, Pharm.D. Candidate

Diabetes is a major global health problem. There are currently 20.8 million people in the United States with diabetes, of which about 6.8 million are not aware that they have the disease.¹ Diabetes is a condition in which the body either does not produce insulin in sufficient concentrations to maintain euglycemia, referred to as Type 1, or does not utilize insulin properly, referred to as Type 2. Poor glycemic control can lead to numerous microvascular and macrovascular complications, which ultimately lead to a shorter lifespan and decreased quality of life.

The treatment of Type 1 diabetes is insulin. There are numerous types of insulins that have different pharmacokinetic properties. Type 2 diabetes treatment consists of oral medications as well as insulin in selected patients.

While treatment of diabetes may lead to better glycemic control, it may increase the risk of hypoglycemia and other side effects including weight gain and skin/injection site reactions. Hypoglycemia can be a devastating consequence of insulin therapy, with consequences for both the patient and the people around them. Patients with diabetes can also develop nocturnal hypoglycemia, which may result in low blood sugars in the morning or a type of rebound hy-

perglycemia (the “Dawn Effect”).

Most type I diabetic patients require some form of basal insulin which works throughout the day to keep glucose levels normal. Most of these basal insulins are subcutaneously injected, and form a crystalline substance which delays absorption. However, these insulins are inconsistently absorbed leading to variability in duration of action and time to onset. Basal insulins may also cause hypoglycemic episodes.

A new type of basal insulin has been approved in the United States. Levemir® (Insulin Detemir) is a long-acting basal insulin that may offer consistent glycemic control while minimizing the risks of hypoglycemia and weight gain generally associated with insulin replacement. The objective of this article is to describe the efficacy and safety of insulin detemir.

Pharmacology

Insulin detemir is produced using recombinant DNA technology. The amino acid residue at position B30 has been omitted and a 14-carbon fatty acid chain has been added to position B29. The fatty acid chain increases lipophilicity and the addition of zinc stabilizes the compound. The formation of insulin

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Table 1. Efficacy of insulin detemir and NPH in adults, adolescents and children with diabetes mellitus.

Reference	Duration (weeks)	Type (1 or 2)	Treatment (no. of pts)	Baseline Mean HbA1c (%)	Baseline FPG (mmol/L)	Mean HbA1c at end of study (%)	Mean FPG (mmol/L) at end of study	Mean Change in Bodyweight From Baseline (kg)
Hermansen et al. ^b	18	1	ID bid ^a (298)	8.48	8.83	7.88***	7.58	-0.95***
			NPH bid ^a (297)	8.29	9.17	8.11	8.10	0.07
Home et al.	16	1	ID bid ^c (137)	8.55	11.57	7.75	9.75**	0.02*
			ID bid ^a (139)	8.74	11.65	7.78	8.94***	0.24*
			NPH bid ^a (132)	8.52	12.20	7.94	11.24	0.86
Russell-Jones et al. ^d	26	1	ID qd ^e (491)	8.35	11.88	8.30	10.27***	-0.23*
			NPH qd ^e (256)	8.35	11.55	8.41	11.40	0.31
Vague et al.	26	1	ID bid ^f (301)	8.18	11.60	7.60	9.2	-0.2***
			NPH bid ^f (146)	8.11	11.60	7.64	9.9	0.7
Haak et al.	26	2	ID qd/bid ^g (341)	7.89	10.11	7.63	9.73	0.9††
			NPH qd/bid ^g (164)	7.77	10.42	7.48	9.61	1.6
			ID qd/bid ^g (195)	8.16		7.46‡	7.28	0.51±¶
Raslova et al.	22	2	NPH qd/bid ^d (199)	8.08		7.52‡	7.32	1.13‡
			ID bid ^f (216)	8.18	11.85	7.53	10.7	-0.1
De Leeuw et al. ¹⁰	52	1	NPH bid ^f (99)	8.03	11.51	8.03	10.8	1.2
Pieber et al. ⁵	16	1	ID bid ^h (139)	8.01	10.00	7.67	9.83***	-0.6***
			ID bid ^a (132)	8.13	10.63	7.65	9.15§	0.01
			NPH bid ^a (129)	8.08	10.65	7.73	11.14	0.7

a Administered in the morning and at bedtime. b Bolus insulin requirements in the NPH group were provided by regular human insulin. c Administered at 12-hour intervals. d Bolus insulin requirements were provided by regular human insulin. e Administered at bedtime. f Administered before breakfast and at bedtime. g Frequency of administration according to previous treatment. h Administered in morning and pre-dinner. * p≤0.05, ** p = 0.004, ***p ≤ 0.001 vs NPH, †† p = 0.02 vs NPH, ‡ p < 0.001 vs baseline, ± p < 0.02, ¶ p = 0.038, § p < 0.006 vs NPH.

hexamers at the site of injection results in delayed dissociation of insulin molecules and slow systemic absorption.²

The mechanism of action of insulin detemir is the same as that of human insulin. It promotes the storage and inhibits the breakdown of glucose, fat, and amino acids. It facilitates the uptake of glucose in muscle and adipose tissue. It inhibits glycogenolysis and gluconeogenesis and enhances the storage of fat and inhibits mobilization of fat for energy in adipose tissue. Insulin is also involved in the regulation of

protein metabolism.³

Pharmacokinetics

Insulin detemir is administered by subcutaneous injection only. It is 98-99% reversibly bound to albumin. The effect of detemir on plasma glucose is dose-dependent. Insulin detemir provides a metabolic effect for up to 24 hours, depending on the dose administered. There is a between-subject variability in the duration of action for insulin detemir, but it is significantly lower than that of NPH insulin.³⁻⁴ Peak

plasma concentrations are reached within 6-8 hours of injection. More than 50% of the maximum effect occurs between 3-4 hours to 14 hours after injection for doses ranging from 0.2-0.4 units/kg.³ Detemir exhibits slightly higher plasma AUC and C_{max} in children compared to adolescents and adults (10% higher, and 24% higher respectively). No dosage adjustment is necessary in children because administration is patient-specific.³ For patients with hepatic impairment, there are no recommendations available. Dosage should be modified depending on clinical response and degree of hepatic impairment. Renal impairment does not appear to alter the pharmacokinetics of insulin detemir, however pharmacodynamic differences occur in insulin sensitivity as renal function declines which result in increased responses to a given dosage.³ As with treatment in individuals with hepatic impairment, dosage should be based on clinical response.³

Clinical Trials

Several clinical trials have assessed the efficacy of insulin detemir. (Table 1) Detemir has been compared to NPH in patients with Type 1 and 2 diabetes. Most regimens included insulin aspart or regular insulin as the meal-time insulin. Most trials demonstrate that insulin detemir provides glycemic control that is similar to or better than NPH insulin in patients with type 1 and type 2 diabetes. Patients on insulin detemir achieved fasting plasma glucose levels that were similar to or lower than those of patients on NPH insulin.

Pieber et al investigated the safety and efficacy of two different administration time regimens with insulin detemir and NPH insulin. Insulin detemir was administered in the morning and pre-dinner or in the morning and at bedtime. The NPH regimen was given in the morning and before bedtime. All subjects were given insulin aspart before meals. All three treatment groups had comparable HbA_{1c} levels after 16 weeks, with reductions of 0.39-0.49%. Lower fasting plasma glucose was recorded with insulin detemir morning and dinner and morning and bedtime compared to the NPH -based regimen. There was significantly less within-person variation in self-measured fasting plasma glucose for the insulin detemir regimens. The overall and nocturnal rate of hypoglycemia was similar among all three groups. Mean bodyweight was lower in the insulin detemir regimens compared to NPH after 16 weeks, suggest-

ing a lesser propensity to induce weight gain with detemir.⁵

De Leeuw et al compared the long term efficacy and safety of a twice-daily insulin detemir regimen with a NPH regimen in type 1 diabetic patients. The HbA_{1c} decreased by 0.64% and 0.56%, respectively. This difference was not statistically significant. Nocturnal hypoglycemia during months 2-12 was 32% lower in the detemir group than the NPH group (p = 0.02). Baseline-adjusted mean body weight was lower in the detemir group after 12 months. There was a between-group difference of 1.44 kg (p = 0.0002), favoring detemir.¹⁰

Haak, et al. compared the safety and efficacy of an insulin detemir regimen with that of NPH-based therapy in type 2 diabetic patients. Both regimens resulted in significant reductions in HbA_{1c} levels. (detemir HbA_{1c}: 0.2, p= 0.004; NPH HbA_{1c}: 0.4, p= 0.0001). Reductions in fasting plasma glucose (FPG) as well as self-monitored blood glucose (SMBG) profiles were similar for both groups. Within-subject day to day variation in fasting SMBG was significantly less with insulin detemir (p=0.021). The detemir regimen resulted in less body weight gain than the NPH regimen (1.0 kg vs. 1.8 kg, p= 0.017).¹¹

Raslova, et al. compared the safety and efficacy of an insulin detemir regimen to that of a NPH regimen in type 2 diabetic patients. Both regimens resulted in comparable reductions in HbA_{1c} (p= 0.515). A significantly lower within-person variation in SMBG (SD: 1.2 mmol/L vs. 1.54 mmol/L, p<0.001), and a lower degree of weight gain was seen in the detemir regimen. (0.51kg vs. 1.13 kg, p=0.038).¹²

Adverse Effects

Hypoglycemia is the most common adverse event associated with detemir. However, the risk of total hypoglycemia is comparable between insulin detemir and NPH insulin. Some studies suggest a lower incidence of nocturnal hypoglycemia with detemir. Within-person variation in SMBG levels are significantly lower in detemir regimens compared to NPH.^{5,6}

Other adverse events reported in clinical trials are headache, upper respiratory tract infection, dizziness, and rhinitis. Most of these adverse events are considered mild and are no considered drug-related. Some patients experience minor local skin

reactions around the injection site.^{5,6,7} Weight gain is a consequence of insulin administration regardless of the specific product. Weight gain associated with insulin detemir is generally less pronounced compared with NPH.⁷

Contraindications and Precautions

Contraindications to treatment include hypersensitivity to detemir or any of its constituents, as well as current hypoglycemia.⁸ Insulin detemir is not intended to be used with an insulin pump. Caution should be used when changing insulin doses. Other precautions include change in physical activity or diet, hepatic or renal impairment, and periods of illness or stress. Detemir should be used in pregnancy and breast-feeding patients only if the benefit outweighs the risks.

Dosing

For once-daily use, detemir should be administered in the evenings or at bedtime. For twice-daily use, the second dose should be administered with dinner, at bedtime, or 12 hours after the first dose. When patients are switching from NPH insulin, higher doses of detemir may be required to reach the same glycemic control. However, switching should be done on a unit-for-unit basis. It should then be titrated to reach target glucose levels. For insulin-naïve patients, who are inadequately controlled by oral antidiabetic drugs alone, insulin detemir should be dosed at 0.1-0.2 units/kg once daily in the evening, or 10 units once or twice daily. The starting dose should then be titrated to reach glycemic targets.⁸

Pricing

Levemir[®] was FDA approved in June 2005 and should be available in 2006. No pricing information is available at this time.

Summary

Insulin detemir is a new type of insulin for use in both type 1 as well as type 2 diabetics. It has a comparable safety and efficacy profile to NPH insulin with less weight gain. It shows value in patients who have questionable compliance due to increased weight gain. Future studies should attempt to compare insulin detemir with insulin glargine to clarify the role of these agents as basal insulin products in patients with diabetes.

References:

1. American Diabetes Association. www.diabetes.org. Accessed: 11/27/05.
2. Hordern, S.V.M.; Russel-Jones, D.L. "Insulin Detemir, Does a New Century Bring a Better Basal Insulin?" *Int J Clin Pract* 2005;59:730-739.
3. Insulin Detemir. *Clinical Pharmacology Online*. Gold Standard.
4. Plank, Johannes MD, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care* 2005;28:1107-1112.
5. Pieber, TR, Draeger E, et al. Comparison of three multiple injection regimens for type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. *Diabetic Medicine* 2005;22:850-857.
6. Chapman, Therese M, Perry, Caroline M. Spotlight on insulin detemir in type 1 and 2 diabetes mellitus. *Biodrugs* 2005;19:67-69.
7. Goldman-Levine, Jennifer D, Lee, Karen W. Insulin detemir— a new basal insulin analog. *Ann of Pharmacother* 2005;39:502-507.
8. Insulin Detemir. Thompson MICROMEDEX. Thompson Healthcare Inc. 2005.
9. Chapman, Therese M. Perry, Caroline M. Insulin Detemir: a review of its use in the management of type 1 and 2 diabetes mellitus. *Drugs* 2004;64:2577-2595.
10. De Leeuw, I; et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obesity and Metabolism* 2005;7:73-82.
11. Haak T, et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obesity and Metabolism* 2005;7:56-64.
12. Raslova K, et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Research and Clinical Practice* 2004;66:193-201.

PHARMACOTHERAPY OF GOUT: AN UPDATE

Adrianna Natoli, Pharm.D. Candidate

Uric acid is an end product of purine nucleo-

tide metabolism. It exists as the urate ion at physiological pH and has a narrow window of solubility. The enzyme, xanthine oxidase converts xanthine to urate. Humans do not express the enzyme uricase responsible for uric acid degradation to allantoin. Once urate has been formed, it can be eliminated via the gastrointestinal tract, kidneys, or can be deposited in tissues. The limit of solubility of monosodium urate (MSU) in serum is 6.4 mg/dL at 37°C. Hence, the “normal” uric acid level in men (7 mg/dL) is at the limits of urate solubility in vitro, and the levels in premenopausal women (6 mg/dL) approach saturation as well, imposing a fragile physiologic urate balance. Hyperuricemia, usually defined as a serum uric acid (SUA) level >7 mg/dL, can be caused by overproduction of urate, or more commonly by insufficient renal excretion.^{1,2,3}

Gout is a systemic rheumatic disease, recognized for centuries, which results from an inflammatory response provoked by deposition of MSU crystals in the articular cartilage and synovial membrane. Demonstration of MSU crystals in the synovial fluid is essential for a definitive diagnosis of gouty arthritis. Left untreated, these crystals can aggregate in joint spaces, causing crippling damage to cartilage and bone and, when deposited in organs such as the kidney, eventually lead to organ dysfunction, particularly renal impairment. The single most important risk factor for the development of gout is an elevated SUA level. Although hyperuricemia is central to gout, by itself it is insufficient to cause the disease, since a substantial number of patients with hyperuricemia never experience an acute flare.

This article will examine the epidemiology and impact of gout as a common clinical problem, followed by the goals of treatment and a review of various options for the pharmacological management of acute gouty attacks, hyperuricemia and chronic gout, as well as prophylactic strategies.

Epidemiology

Gout is an increasingly prevalent medical problem, affecting greater than 1 percent of men in Western countries, with a male:female ratio between 7:1 and 9:1.¹ Gouty arthritis is, in fact, the most common inflammatory joint disease affecting men over 40 years of age.² The incidence of gout increases with age and it has been found to be more prevalent in African Americans than in Caucasians.⁴ A review of the self-reported incidence of gout from

the National Arthritis Data Workgroup estimates that gout affects 2.1 million US citizens. The annual economic burden for new cases of acute gout among US men is \$27.4 million. As the disease progresses it markedly impairs quality of life and ability to work, and its long-term management leads to substantial health care costs, both direct and indirect (e.g., lost productivity).⁴

Treatment Overview

Gout has four stages: (i) asymptomatic hyperuricemia; (ii) acute gouty arthritis; (iii) intercritical gout (intervals between acute attacks) and (iv) chronic tophaceous gout.² The classic symptoms of gouty arthritis are recurrent attacks of acute, extremely painful monoarticular or oligoarticular inflammation; although, polyarthritis can occur as well.

Management of gout involves not only treating acute arthritic inflammation, but also preventing recurrent attacks and disease progression.¹ Hence, there are three stages in the management of gout: (i) treating the acute attack; (ii) lowering urate levels to prevent flares of gouty arthritis and prevent tissue deposition of MSU crystals; and (iii) prophylactic therapy to prevent recurrent attacks and progression.² Current treatment for acute and chronic gout, is based more on practitioners' experience and preferences than on evidence based medicine.^{1,2}

Treatment of Acute Gouty Arthritis

Acute gout is spontaneous and self-limited in nature. The primary goal of therapy in acute gout is to quickly and safely resolve pain and restore functioning. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the preferred treatment in acute gout, unless there are risk factors for their use, i.e. age >65 years; creatinine clearance (CrCl) <50 mL/min; poorly controlled congestive heart failure; history of peptic ulcer disease; anticoagulation therapy; or hepatic dysfunction. These patients are at higher risk of adverse effects associated with use of NSAIDs such as gastropathy, nephropathy and liver dysfunction. Therapeutic success with NSAIDs lies not in which NSAID is chosen, but rather how soon NSAID therapy is initiated after onset of an attack. NSAIDs provide significant symptom relief within 24 hours. NSAIDs should be initiated immediately after the onset of symptoms at maximal doses and then tapered quickly after complete resolution of the attack.^{1,2} A head-to-head comparison of etoricoxib and

indomethacin in patients with acute gout showed similar efficacy suggesting that selective COX-2 inhibitors may provide a reasonable alternative for patients at high risk of gastrointestinal bleeding.⁶ (Table 1). However, COX-2 inhibitors should be used with caution in patients at high risk of cardiovascular disease, and they are no safer than conventional NSAIDs with regard to renal function, blood pressure, or heart failure.

Colchicine is an alternative for the management of inflammation in acute gout. The mechanism of action in gout is interference with formation of tubulin dimers and subsequent leukocyte function, including diapedesis, lysosomal degranulation, and chemotaxis.³ Because it is poorly tolerated, it is not the preferred drug for the treatment of acute gout. An as needed supply of colchicine can be provided to treat acute attacks rapidly at the onset of symptoms. Its effectiveness is highest during the first 12-24 hours of symptoms. In a placebo-controlled trial, approximately two-thirds of patients with acute gout responded to colchicine within hours when the drug was initiated in the first 24 hours of the attack.⁵ However, greater than 80% of patients suffered gastrointestinal adverse effects including nausea, vomiting, diarrhea and abdominal pain with administration of oral colchicine before experiencing complete clinical improvement. This narrow benefit to adverse effect ratio limits the use of colchicine. Colchicine exhibits the poorest ratio of benefit to toxicity of all the agents used in the management of gout.^{1,2} (Table 1).

While intravenous colchicine can quickly abort a gouty attack, its use is discouraged because it has been associated with severe complications, including fatalities. Serious adverse effects include granulocytopenia, disseminated intravascular coagulation, renal failure, hepatocellular toxicity, seizures and shock. These adverse events can occur even at low doses in patients who have impaired elimination of colchicine including those with renal insufficiency, hepatic dysfunction, biliary obstruction and the elderly. Colchicine is not dialyzable and treatment of colchicine intoxication is largely supportive.^{1,2} The maximum recommended intravenous dose of colchicine per flare is 4 mg in adults, whereas in the elderly 2 mg should not be exceeded. Furthermore, additional colchicine should not be administered within 7 days.

Corticosteroids can be considered in those

patients in whom NSAIDs and colchicine are not appropriate. Corticosteroids can be given orally, intravenously, intramuscularly, or intrarticularly. Intrarticular injections of depot corticosteroids are considered beneficial in gouty attacks when only one or two large joints are affected. In this setting, the efficacy of corticosteroids can be secured, while the systemic adverse effects are avoided. It is crucial to ensure that the joint is not infected prior to injecting intra-articular corticosteroids. Systemic corticosteroids must be given at relatively large doses to treat acute gout effectively (i.e. 40-60 mg of prednisone daily initially) and then tapered slowly to prevent rebound flares. (Table 1) Use of parenteral corticosteroids confers no advantage over oral administration unless the patient is unable to tolerate oral medications. Corticotropin has been shown to be effective within hours for both monoarticular and polyarticular gout. Its peripheral anti-inflammatory effects mediated by local activation of the melanocortin type 3 receptor, as well as, the induction of adrenal corticosteroid release are believed to contribute to corticotropin's rapid, marked efficacy in treating acute gouty attacks. Corticotropin is administered as a single SC or IM injection; however, some patients may require a second dose if response is incomplete. Adjunctive treatment with low-dose colchicine has been advocated for the management of rebound flares associated with use of systemic corticosteroids and corticotropin in acute gouty attacks.

Long-Term Treatment of Gout

Gout is not always progressive in nature and attacks are often infrequent, self-limited and easily treated. In patients with hyperuricemia, SUA levels may return to normal when risk factors are modified, such as minimizing alcohol use, discontinuing thiazide diuretics, or losing weight. The primary indications for chronic uric acid-lowering therapy are macroscopic subcutaneous tophi, frequent gouty attacks (>3 per year), or documented uric acid overproduction. Urate-lowering therapy has been found to be cost effective in patients with greater than 2 attacks per year.⁴ When indicated, long-term management of hyperuricemia is crucial to preventing recurrent gouty attacks and the consequences of chronic hyperuricemia such as chronic tophaceous gout, urate nephropathy and urolithiasis. Optimal treatment maintains SUA level below 6 mg/dL rather than just within the "normal" range. Initiation of uric-acid

Table 1. Systemic pharmacological therapy for acute gouty arthritis.

Drug	Dose	Adverse Events	Comments	Cost
NSAIDS				
Naproxen	750-1000mg PO daily x 3 days, then 500-750mg daily x 4-7 days (in 2 divided doses)		Cost saving; avoid in patients with renal or hepatic failure and patients at risk for major GI events, hemorrhage CHF or asthma; interacts with warfarin	\$0.27/ 250 mg tablet
Indomethacin	150-200mg PO daily x 3 days, then 100mg daily x 4-7 days (in 2-4 divided doses)	Gastropathy, renal insufficiency nephropathy, hepatic dysfunction, CNS dysfunction, reversible platelet dysfunction, fluid overload in CHF patients	Avoid in patients with renal or hepatic failure and patients at risk for cardiovascular events, CHF or asthma; aspirin counteracts gastroprotective effect	\$0.32/ 50 mg capsule
Cedlecoxib	400mg PO on day 1, then 200mg daily x 6-10 days (in 2 divided doses)			\$3.17/200 mg capsule
Corticosteroids				
Prednisone	40-60mg PO daily x 3 days, then decrease by 10-15mg/day every 3 days	Fluid retention, mood changes, insomnia, lethargy, appetite stimulation, weight gain, increased BP, acne hyperglycemia.	Avoid if joint sepsis not excluded Avoid in patients subject to hyperglycemia	\$0.20/ 10 mg tablet
Triamcinolone acetonide	60mg IM x 1			
Corticotropin				
	25 USP units SQ for small joints or monoarticular gout 40 USP units IM/IV x 1 for large joints or polyarticular gout	Similar to corticosteroids, but less pronounced	Not universally available Less effective in patients receiving long-term steroids	\$3.17/unit
Colchicine				
	In acute episodes of gout within the first few hours: 0.6mg PO every hour up to 3 hours (max 3 pills) For prophylaxis against acute gout, particularly before initiation of anti-hyperuricemic therapy: CrCl \geq 50ml/min: 0.6mg PO BID CrCl 35-49ml/min: 0.6mg PO daily CrCl 10-34ml/min: 0.6mg PO every 2-3 days Avoid if CrCl <10ml/min or on hemodialysis Reduce doses by 1/2 if \geq 70 years old	Oral: nausea, vomiting, diarrhea, abdominal pain, myopathy (more likely with concomitant cyclosporine or statin therapy and in patients with renal insufficiency IV: tissue necrosis, disseminated intravascular coagulation, granulocytopenia, renal failure, hepatic necrosis, death	Not recommended long-term due to lower benefit to toxicity ratio compared to other treatments Less effective after first day of acute attack Avoid IV administration Drug interactions with erythromycin, statins and cyclosporine can increase risk of toxic effects	\$0.18/ 0.6 mg tablet

lowering therapy should be avoided during the inflammatory phase of acute gout, as it could potentially worsen arthritis. The urate-lowering medications used to treat chronic gout include the uricosuric drugs and xanthine oxidase inhibitors.^{1,2}

Determining 24-hour urinary urate excretion can help identify patients who overproduce urate.

Overproduction occurs when daily urinary urate excretion exceeds 800-1000 mg. Such a diagnostic procedure also helps identify patients in whom uricosuric drugs would be contraindicated due to a heightened risk of urolithiasis. However, the test cannot identify patients in whom hyperuricemia is a result of a combination of urate overproduction and under-

excretion, and cannot reliably identify urate overproduction in patients with creatinine clearance below 60 mL/minute. Despite these limitations, it is advisable to collect and evaluate a 24-hour urine test to identify urate overproduction in the absence of an obvious cause of hyperuricemia, such as diuretic use or renal failure.^{1,2} However, 24-hour urine urate levels are infrequently evaluated since >90% of patients with hyperuricemia underexcrete uric acid and because SUA will respond to allopurinol regardless of the etiology.

Uricosuric Drugs

Uricosuric drugs are considered first-line therapy in patients with hyperuricemia due to renal urate underexcretion. Uricosuric drugs inhibit post-secretory renal proximal tubule reabsorption of uric acid, increasing its renal clearance, and, thus, reducing SUA. Upon the initiation of uricosuric drugs, intense uricosuria can result in urolithiasis and worsening renal function. Hence, uricosuric drugs are initiated at low doses and gradually titrated over 2-6 weeks. The risk of urolithiasis can also be minimized by having patients stay well hydrated and alkalinizing the urine with administration of sodium bicarbonate.

Probenecid is an effective uricosuric agent in patients with normal renal function and no history of renal stones or massive tophi. Sulfapyrazone is not universally available and is not considered a first-line uricosuric agent secondary to its adverse effect profile, including increased risk of bleeding and bone marrow suppression.

Use of low doses (<500 mg) of aspirin can interfere with the uricosuric effect of these agents and should be addressed before starting a uricosuric. Fenofibrate, a fibric acid derivative, has been shown to have a uricosuric effect independent of its lipid-lowering effect and is associated with a SUA reduction of 20-35%. It may be beneficial in patients with gout who also have dyslipidemia. Losartan, an angiotensin II receptor antagonist, reduces SUA levels, but, unlike other uricosurics, it simultaneously increases urine pH, thereby, reducing the risk of urolithiasis. Losartan's uricosuric effect is independent of its hypertensive effects through angiotensin receptor antagonism. It may be particularly beneficial in patients with gout who have hypertension. (Table 2)

Uricostatic Drugs

Xanthine oxidase inhibitors are uricostatic drugs, which inhibit uric acid synthesis. Xanthine oxidase inhibitors interfere with the conversion of hypoxan-

thine to xanthine and of xanthine to uric acid, causing a decrease in SUA and uric acid levels, and an increase in serum and urinary hypoxanthine and xanthine levels.²

Allopurinol is a structural analogue of hypoxanthine. Its uric acid-lowering effect is dose-dependent. Although most patients are maintained on a fixed dose of allopurinol, it should be titrated as tolerated to the SUA level to ensure that SUA levels are kept low enough to help prevent further attacks. Allopurinol is dosed once daily and is effective irrespective of the cause of hyperuricemia, making it the most commonly prescribed urate-lowering agent. However, one of its disadvantages is that it has several important drug interactions. For instance, allopurinol may interfere with hepatic metabolism of oral anticoagulants, and its administration with agents such as mercaptopurine and azathioprine may result in serious hematologic complications if the dose of these medications is not reduced, as they are inactivated by xanthine oxidase. Furthermore, up to 5% of patients are unable to tolerate allopurinol due to its adverse effects (Table 3).² Of greatest concern is the potential for severe, life-threatening rash, which is more common in patients with renal dysfunction when the dose is not adjusted.

Oxypurinol is the active metabolite of allopurinol, the agent primarily responsible for allopurinol's clinical effect of inhibiting xanthine oxidase. Its most significant role is in patient's who are allergic to allopurinol. Though oxypurinol is not commercially available in the US, it can be obtained through the manufacturer (ILEX Oncology, San Antonio, TX) for compassionate use (Table 2).²

Febuxostat is a novel, orally administered, nonpurine selective inhibitor of xanthine oxidase currently in phase III studies as a potential alternative to allopurinol for patients with hyperuricemia and gout. Though it is a potent inhibitor of xanthine oxidase, it has minimal effects on other enzymes involved in purine and pyrimidine metabolism. The recently published Febuxostat versus Allopurinol Controlled Trial (FACT), a large, phase 3, randomized, double-blind, multi-center, non-inferiority trial compared febuxostat and allopurinol with regard to safety, urate-lowering efficacy, and incidence of flares and number of tophi in adult subjects with hyperuricemia and gout. Investigators showed that at all ranges of initial urate levels, the primary efficacy endpoint, serum urate level below 6 mg/dL, was

Table 2. Pharmacological treatments for hyperuricemia and chronic gout.

Drug	Pharmacokinetics	Adverse events	Dose	Cost
Uricosuric Drugs				
Probenecid	Good GI absorption; $t_{1/2}$ of 6-12 hours; 40% renal excretion within 48 hours	Precipitation of acute gout, urolithiasis, impairment of renal function	Starting dose: 250mg PO BID, gradually increased to 1000mg BID (maximal dose to target SUA level <6mg/dL in patients with normal renal function)	\$0.58/500mg tablet
Sulfinpyrazone	Short $t_{1/2}$ requires BID dosing; congener of phenylbutazone (can induce peptic ulcer and bone marrow suppression)	Precipitation of acute gout, urolithiasis, impaired renal function; inhibits platelet function (increased risk of bleeding with warfarin); use limited by adverse events	Starting dose: 50mg PO BID; gradually increased to 100-400mg PO daily (in 2 divided doses); Maximal dose to target SUA level <6mg/dL in patients with normal renal function	\$0.60/100mg tablet
Micronized Fenofibrate	30% more bioavailable than non-micronized; meals increase absorption	Nausea, vomiting, constipation, flatulence, dyspepsia; cholelithiasis; elevated serum transaminases, myopathy	200mg PO daily	\$3.13/200mg capsule
Losartan	Metabolite E 3174 inhibits renal tubular absorption of uric acid	Diarrhea, dyspepsia, dizziness, cough, upper respiratory infections	50mg PO daily	\$1.83/50mg tablet
Xanthine Oxidase Inhibitors				
Allopurinol	Short $t_{1/2}$ of 40 minutes; metabolized to oxypurinol by xanthine oxidase; maximum SUA lowering within 14 days	GI irritation, bone marrow suppression, precipitation of acute gout, pruritis; hypersensitivity syndrome (skin rash to life-threatening) Toxicity similar to allopurinol in 30% patients	50-300mg PO daily CrCl \geq 90ml/min: 300mg daily CrCl \geq 60ml/min: 200mg daily CrCl \geq 30ml/min: 100mg daily CrCl \leq 30ml/min: 50-100mg daily	\$0.14/100mg tablet
Oxypurinol	Active metabolite of allopurinol; $t_{1/2}$ 9-15 times longer than allopurinol		Not available – compassionate use only	N/A
Febuxostat	Metabolism primarily hepatic, renal impairment does not impact serum urate lowering effect	Diarrhea, headache, nausea, liver function test abnormalities	80 or 120mg PO daily	Not yet available

reached by significantly higher proportions of subjects receiving daily febuxostat (80 or 120 mg) than subjects receiving allopurinol (300 mg). This difference was sustained at all visits through the 52 weeks of the study. There was no significant difference among the groups in incidence of acute gouty flares or reduction in the number of tophi. One limitation in this study was that the dose of allopurinol was fixed and patients were not titrated to target SUA levels.

The incidence of adverse events was similar among treatment groups, and most adverse events were mild to moderate in severity. The rates of discontinuation were similar in the 80 mg febuxostat and the allopurinol groups, but significantly higher in the 120 mg febuxostat group ($p=0.003$) due to a higher incidence of gout flares and adverse events in this group. The study concluded that febuxostat, at a

daily dose of 80 mg or 120 mg was more effective than allopurinol at the fixed daily dose of 300 mg in lowering SUA levels. FACT also demonstrated that maintaining the SUA concentration below 6 mg/dL resulted in a greater reduction in gouty flares and tophi, supporting a subsaturating range of less than 6 mg/dL as the target for management of hyperuricemia. Though treatment-related adverse events were similar for all groups in this study, long-term studies are ongoing to provide further data on the safety profile of febuxostat.⁶

Uricosuric Drugs

Humans lack urate oxidase, the enzyme responsible for oxidation of urate into the highly soluble and readily excreted allantoin. Unlike, xanthine oxidase inhibitors that inhibit uric acid synthesis, urate oxidase also breaks down pre-existing uric acid. Ras-

buricase (Elitek[®]) is a recombinant form of urate oxidase. Rasburicase catalyzes enzymatic oxidation of uric acid into allantoin, thus lowering elevated SUA levels. Rasburicase has been primarily studied in pediatric patients with hematological malignancies or solid tumors receiving anti-cancer agents that increase the risk for tumor lysis syndrome (TLS). Long-term urate oxidase treatment in gout has not been studied. The use of urate oxidase preparations in patients with chronic gout is limited by the need for parenteral administration, as well as the inherent antigenicity of this product. Production of anti-urate oxidase antibodies and decreased effectiveness has been documented following its administration.²

Prophylactic Therapy

Colchicine is commonly used as prophylaxis against recurrent acute gout, as such episodes are common during initial treatment with uric acid-lowering treatment. A standard approach is to use low-dose oral colchicine (0.6 mg orally twice a day) for the first six months of anti-hyperuricemic therapy in patients with normal renal function. Lower doses are required to adjust for renal dysfunction and in elderly patients. However, even low doses of daily colchicine may be associated with severe adverse effects such as myopathy and myelosuppression. Furthermore, the effectiveness of colchicine as a single-drug therapy for prophylaxis of acute gouty arthritis has not been confirmed by placebo-controlled trials. Another option for prophylaxis is administration of low-dose NSAIDs. However, data supporting this practice are sparse, and there are no comparative studies with colchicine.^{1,2} Nevertheless, NSAIDs may be used as prophylaxis in patients who do not tolerate or are not candidates for colchicine.

Summary

The goal of therapy in acute gout is rapid, safe resolution of pain and inflammation. NSAIDs are considered first-line therapy for the treatment of acute gout in patients without contraindications to their use normal renal function and who have low risk for gastrointestinal or cardiac toxicity. Colchicine is an alternative to NSAIDs. Corticosteroids, corticotrophin, and selective COX-2 inhibitors are options in select patients.

Long-term uric-acid lowering therapy is appropriate in patients with tophi, frequent attacks of gouty arthritis (>2 per year), or documented overpro-

duction of urate, though it should not be initiated during an acute attack. The target uric acid level for uric-acid lowering therapy is less than 6 mg/dL. Allopurinol is the drug of choice for initial uric-acid lowering therapy. Uricosurics such as probenecid, micronized fenofibrate, and losartan may be used in allopurinol-allergic patients with uric acid underexcretion and normal renal function. If there are no contraindications, colchicine or NSAIDs can be considered for short-term concomitant prophylaxis against gouty attacks during the initiation of uric-acid lowering therapy. Non-pharmacological measures are an important adjunct to pharmacotherapy and should include limiting alcohol intake, maintaining a low-purine diet and treating comorbid conditions such as obesity, hypertension, hyperlipidemia, and coronary artery disease.

References

1. Terkeltaub RA. Clinical practice: gout. *N Engl J Med* 2003;349:1647-55.
2. Schlesinger N. Management of acute and chronic gouty arthritis: present state of the art. *Drugs* 2004;24:2399-2416.¹
3. Cannella AC, Mikuls TR. Understanding treatments for gout. *Am J Manag Care* 2005;11:S451-58.
4. Brixner DI, Ho MJ. Clinical, humanistic, and economic outcomes of gout. *Am J Manag Care* 2005;11:S459-64.
5. Ahern MJ, Reid C, Gordon TP, et al. Does colchicine work? The results of the first controlled study in gout. *Aust N Z J Med* 1987;17:301-4.
6. Schumacher HR Jr, Boice JA, Daikh DI, et al. Randomized double blind trial of etoricoxib and indomethacin in treatment of acute gouty arthritis. *BMJ* 2002;324:1488-92.
7. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005; 353:2450-61.

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