Benzbromarone withdrawn from the European market: Another case of "absence of evidence is evidence of absence"?

Sirs,

Gout, already described by Hippocrates, has been one of the most curable disorders of modern rheumatology for years due to potent urate lowering therapeutic options. While in only a minority of our rheumatologically pre-selected patients xanthine oxidase inhibition by allopurinol lowered serum uric acid (SUA) levels sufficiently to prevent gouty attacks, in non-preselected gouty patients 300 mg allopurinol normalized SUAin 85% of patients (1, 2). In most cases gout is caused by inadequate, low uric acid excretion, explaining why uricosuric agents have long been considered the first choice treatment option by many but not all rheumatologists. Not only for reasons of pathophysiology in low excretor gout, but also due to potential hazards associated with the combination of azathioprine and allopurinol, which is clearly not the case when azathioprine is combined with benzbromarone.

Exactly how low should SUA levels become in order to deplete crystal stores and prevent attacks (3)? Li-Yu *et al*. have demonstrated that aiming at SUA levels < 0.36 mM may be suboptimal (3), but it is often clinically quite adequate to aim for levels of < 0.30 mM (2). This is comprehensible when studying the chemico-physical data (4). Perez-Ruiz *et al*. demonstrated in a head-to-head comparison that allopurinol is inferior to benzbromarone in reducing SUA (5). We found similar results in 85 gout patients: SUA levels < 0.30 mM are reached in 79% by benzbromarone monotherapy (100 mg daily), and in just 10% by allopurinol monotherapy (200 mg daily). This may explain why in Europe we all were quite happy with benzbromarone.

Therefore, why was there a sudden withdrawal of this compound from the European market in 2003? Did Sanofi-Synthelabo fear a lawsuit? Or was it due to the lack of commercial profitability?

A PubMed search for fatal outcomes with the main urate lowering treatment options provides us no significant clue (Table I). There are only sporadic reports of hepatic failure secondary to benzbromarone (6); the incidence was about 2 cases per 400 million Europeans, i.e. 1:100,000 benzbromarone prescriptions. Was this the argument for Sanofi-Synthelabo, which owns the patent and therefore has a monopolist position with regard to benzbromarone, to stop its production? In April 2003 the Netherlands Medicine Evaluation Board (MEB) agreed with the request by Sanofi to stop benzbromarone production for the Dutch market, which took place simultaneously in most European countries. In most European countries neither the uricosuric probenecid nor sulfinpyrazone have been registered for the treatment of gout. An alternative regimen was suggested despite the aforementioned reports in the literature (5): allopurinol, on strict indication combined with probenecid. A peculiar advice since probenecid has not been registered at all in The Netherlands for the treatment of gout.

Table I. A PubMed search (excluding Japanese papers) for fatal outcome using 4 treatment options: allopurinol, probenecid, benzbromarone, and sulfinpyrazone.

Fatal/death	No. of papers	No. of cases	Year of publication
Allopurinol[a]	14	14	1970-2001
Probenecid[b]	1	1	1957
Benzbromarone[c]	2	3	1995-2000
Sulfinpyrazone[d]	0	0	1976-2004

European registration status: [a]Fully registered for gout.
[b]Registration previously held by MSD, withdrawn due to lack of profitability in the past, but often applicable on special request.
[c]Up to 2003, registration in all of Europe, England excluded. From January 2004 registered only in Spain, and in The Netherlands for strict indications only, i.e. for allopurinol intolerant/allergic gouty patients. [d]Registration held by Novartis (Anturane®) only in England and Ireland, withdrawn from the market in Spain, not registered in other European countries and therefore generally not applicable.

In clinical practice general practitioners and rheumatologists were left stunned. A lobby by general practitioners and the Dutch Association of Rheumatology has therefore recently brought our MEB to request the pharmaceutical company to restart benzbromarone production for the Dutch market, and their request remarkably was granted. From January 2004 Dutch gouty patients again have the opportunity to be treated with the potent uricosuric benzbromarone. Interestingly, the registration of benzbromarone only has been granted for cases with allopurinol intolerance. But generally allopurinol is well tolerated; only in about 2% of cases, in particular elderly individuals with renal dysfunction, is a pruritic maculopapular eruption with or without fever and facial/tongue swelling encountered. Only for this small group of gout patients will benzbromarone be an option once again according to Sanofi and the Netherlands MEB.

Why did our European MEBs agree so easily with the pharmaceutical company's request to stop a generally safe treatment option? Medico-legal and commercial reasons must cross our minds. One could speculate about a novel class of benzbromarone derivatives on the horizon (7), as the commercial profitability of benzbromarone may be low. If the pharmaceutical company is driven to prevent potential claims in the future, then other companies might follow a similar procedure. This case could serve as a warning for our European MEBs not to bury older drugs before breeding new baby drugs.

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References

1 DAY RO, MINERS JO, BIRKETT DJ *et al*.: Allopurinol dosage selection: relationships between dose and plasma oxypurinol and urate concentrations and uinary urate excretion. *Br J Clin Pharmacol* 1988; 26: 423-8.
2 FAM AG: Hyperuricemia and gout. *In* RAKEL RE (Ed.): *Conn's Current Therapy*, 51st ed., Philadelphia, W.B. Saunders Co., 1999; 561-6.
3 LI-YU J, CLAYBURNE G, SIECK M *et al*.: Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? *J Rheumatol* 2001; 28: 577-80.
4 ALLEN DJ, MILOSOVICH G, MATTACKS AM: Inhibition of monosodium urate crystal growth. Arthritis Rheum 1965; 8: 1123.
5 PEREZ-RUIZ F, ALONSO-RUIZ, CALABOZO M *et al*.: Efficacy of allopurinol and benzbromarone for the control of hyperuricemia. A pathogenic approach to the treatment of primary chronic gout. *Ann Rheum Dis* 1998; 57: 545-9.
6 VAN DE KLAUW MM, HOUTMAN PM, STRICKER BH *et al*.: Hepatic injury caused by benzbromarone. *J Hepatol* 1994; 20: 276-9.
7 LOCUSON CW, WAHLSTROM JL, ROCK DA *et al*.: A new class of CYP2C9 inhibitors: probing 2C9 specificity with high affinity benzbromarone derivatives. *Drug Metab Dispos* 2003; 31: 967-71.

Polymyositis associated with HIV infection during immune restoration induced by highly active anti-retroviral therapy

Sirs,

Polymyositis associated with human immunodeficiency virus (HIV) infection was first described in 1983, and many reports in the past several years have confirmed this pathologic association (1, 2). It usually occurs early in the course of HIV disease, but may presents at all stages, has a relatively good prognosis, responds well to immunosuppressive therapy, and has little evidence of adverse outcome on the HIV infection (3, 4). However, it is often difficult to distinguish HIV-related polymyositis from myo-

pathy associated with nucleoside reverse-transcriptase inhibitor (NRTI) therapy and mitochondrial dysfunction.

Patient 1. A 52-year-old, homosexual, male patient with HIV infection diagnosed since eight years, was admitted owing to a four-month history of intermittent myalgia, muscular fatigue, and progressive muscle weakness in his upper and lower limbs, but maximal in proximal muscles of the legs. Antiretroviral therapy was started since five years, and the most recent antiretroviral regimen included zidovudine, lamivudine and lopinavir/ritonavir, and was administered since ten months.

The admission laboratory workout revealed increased serum levels of creatine phosphokinase or CK (622 U/L), lactate dehydrogenase or LDH (705 U/L), aspartate aminotransferase or AST (82 U/L), and aldolase (14.3 U/L). Immunological and virological tests demonstrated a CD4+ lymphocyte count of 541 cells/mm^3, with a plasma viral load (HIV RNA) lower than 50 copies/mL. Physical examination showed diffuse muscle hypotrophy and asymmetric hyposthenia affecting the proximal and distal muscle groups in both upper and lower extremities, associated with raising tendon reflexes. Sensory examination and coordination were normal.

An electromyogram revealed myopathic motor unit potentials showing early recruitment and full interference patterns, as well as fibrillation potentials and positive sharpe waves, indicative of an irritative process. A biopsy specimen of quadriceps muscle showed diffuse necrotic and degenerative alterations of muscle fibers in association with broad interstitial inflammatory infiltrates, including mostly macrophages, lymphocytes, and plasma cells. HIV-associated polymyositis was diagnosed and therapy with oral prednisone (0.5 mg/Kg daily) was begun.

Six months later, the patient reported a mild subjective benefit and the dose of prednisone was decreased to 0.25 mg/Kg daily. One year later, he did not report any symptoms of myositis; physical examination, electromiography and laboratory workout were normal.

Patient 2. A 51-year-old drug abuser male patient with advanced HIVinfection recognized since 13 months and Graves' disease diagnosed since six months, was admitted owing to the persistence of asthenia and progressive muscle weakness in his upper and lower extremities, associated with dysphagia to solids and liquids. Physical examination revealed muscle hypotrophy and asymmetric hyposthenia affecting mostly proximal muscle groups in both upper and lower limbs and neck, while sensory evaluation and coordination did not show any alteration. Swallowing assessment confirmed severe oropharingeal muscle weakness. Ongoing antiretroviral theraphy included zidovudine, lamivudine, and nelfinavir, and was started 12 months before the ospitalization.

The laboratory workout showed increased serum levels of CK (485 U/L), LDH (692 U/L), AST (91 U/L), and aldolase (13.2 U/L). Immuno-virological tests showed a CD4+ lymphocyte count of 348 cells/mm^3 and a plasma HIV viral load lower than 50 copies/mL. Electromyography revealed diffuse fibrillation and severe reduction of muscle action potential amplitudes bilaterally. A biopsy specimen of quadriceps muscle showed frank necrotic changes of muscle fibers infiltrated by inflammatory cells, mainly lymphocytes and plasma cells. HIV-associated polymyositis was diagnosed and therapy with oral prednisone (0.5 mg/Kg daily) was started.

Six months later, the patient referred a remarkable improvement of muscle weakness and dysphagia. One year later, he was asymptomatic and electromiography was normal, such as the serum levels of muscular enzymes.

Polymyositis is considered the most common of the HIV-associated myopathies and usually shows clinical course, laboratory and electromyographic findings similar to the idiopathic form observed in HIV-negative subjects.

The pathophysiology of HIV-associated polymyositis is unknown still today. Several studies suggested that HIV-associated myositis is not attributable to persistent HIV infection of the muscle cells (5). However, other authors have found amplified HIV nucleic acids in myocyte nuclei, leading to the opposite conclusion (6).

At the same time, the rapid onset of HIV-associated polymyositis during the immune restoration following the use of combination antiretroviral therapy which has described in some reports supports the immunopathological mechanism of HIV-related myositis, similarly to other autoimmune manifestations seen in HIV-positive patients receiving HAART(3, 7).

HIV-polymyositis is often difficult to distinguish from the NRTI-related myopathy. Ragged-red fibers, abnormal mitochondrial levels in muscle tissue, concurrent manifestations of mitochondrial toxicity (such as hyperlactataemia, peripheral neuropathy, liver toxicity, acute pancreatitis, or pancytopaenia), and the disease reversibility after the discontinuation of drug therapy suggest a diagnosis of NRTI-associated myopathy. Particularly, a recent report highlights the importance of muscle biopsy in HIV-positive subjects whose myopathy persists despite withdrawal of antiretroviral therapy (8, 9).

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References

1. CUELLAR ML: HIV infection-associated inflammatory musculoskeletal disorders. *Rheum Dis Clin ics North Am* 1998; 24: 403-21.
2. MOYLE G: Clinical manifestations and management of antiretroviral nucleoside analog-related mitochondrial toxicity. *Clin Ther* 2000; 22: 911-36.
3. JOHNSON RW, WILLIAMS FM, KAZI S, DIMANCHKIE MM, REVEILLE JD: Human immunodeficiency virus-associated polymyositis: a longitudinal study of outcome. *Arthritis Rheum* 2003; 49: 172-8.
4. SOLINGER AM: Rheumatic manifestations of human immunodeficiency virus. *Curr Rheumatol Rep* 2003; 5: 205-9.
5. LEON-MONZON M, LAMPERTH L, DALAKAS M: Search for HIV proviral DNA and amplified sequences in the muscle biopsies of patients with HIV polymyositis. *Muscle Nerve* 1992; 16: 408-13.
6. SEIDMAN R, PERESS NS, NUOVO GJ: *In situ* detection of polymerase chain reaction-amplified nucleic acids in skeletal muscle in patients with myopathy. *Mod Pathol* 1994; 7: 369-75.
7. SELLIER P, MONSUEZ JJ, EVANS J *et al*.: Human immunodeficiency virus-associated polymyositis during immune restoration with combination antiretroviral therapy. *Am J Med* 2000; 109: 510-2.
8. PRIME KP, EDWARDS SG, PAKIANATHAN MR, HOLTON JL, SCARAVILLI F, MILLER RF: Polymyositis masquerading as mitochondrial toxicity. *Sex Transm Infect* 2003; 79: 417-8.
9. AUTRAN B, CARCELAIN G, LI TS *et al*.: Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIVdisease. *Science* 1997; 277: 112-6.

Multiple sclerosis and the antiphospholipid (Hughes) syndrome: Acommon differential diagnosis?

Sirs,

The antiphospholipid (Hughes) syndrome (APS), a prothrombotic disorder, is characterised by prominent neurological involvement. In addition to stroke, headache and memory loss, other features can include ataxia, diplopia, visual loss and myelopathy (1). It is not surprising therefore that some patients with Hughes syndrome are misdiagnosed as multiple sclerosis (MS).

In a recent study from our unit (2), 27 patients with Hughes syndrome who had been originally diagnosed as MS were analysed. The clinical similarities between APS and MS were striking, and brain magnetic resonance imaging appearance was often indistinguishable. Notably, the majority of primary APS patients, once adequately treated with aspirin or anticoagulants, suffered no further neurological episodes.

Two hundred and eighty-two consecutive patients with systemic lupus erythematosus (SLE) and/or APS were asked the standard