Benzbromarone withdrawn from the European market: Another case of "absence of evidence is evidence of absence"?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 SUA in 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 benzbro- 
marone. Exactly how low should SUA levels be- come 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 chemo-physical data (4). Perez-Ruiz et al. demonstrated in a head-to-head comparison that allopurinol is inferior to benzbro- 
marone in reducing SUA (5). We found similar results in 85 gout pa- tients: SUA levels < 0.30 mM are reached in 79% by benzbro- 
marone 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 benzbro- 
marone. Therefore, why was there a sudden with- 
drawal of this compound from the Europe- 
an 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 benzbro- 
marone (6); the incidence was about 2 cases per 400 million Europeans, i.e. 1:100,000 benzbro- 
marone prescriptions. Was this the argument for Sanofi-Synthelabo, which owns the patent and therefore has a monopolist position with regard to benzbro- 
marone, to stop its production? In April 2003 the Netherlands Medicine Evaluation Board (MEB) agreed with the request by Sanofi to stop benzbro- 
marone 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 regi- men was suggested despite the aforemen- tioned reports in the literature (5): allopuri- 

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

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<thead>
<tr>
<th>Year of</th>
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<th>Fatal/death No. of</th>
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<th>Fatal/death No. of</th>
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<td>cases</td>
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<td>Allopurinol</td>
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<td>Probenecid</td>
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<td>Benzbromarone</td>
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<td>3</td>
<td>1995-2000</td>
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<tr>
<td>Sulfinpyrazone</td>
<td>0</td>
<td>0</td>
<td>1976-2004</td>
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European registration status: *Fully registered for gout.

Registration previously held by MSD, withdrawn due to lack of profitability in the past, but often applicable on spe-

References
5. PEREZ-RUIZ F, ALONSO-RUIZ, CALABOZO M et al.: Efficacy of allopurinol and benzbro- 
6. VAN DE KLAAUW MM, HOUTMAN PM, STRICK- ER BH et al.: Hepatic injury caused by benzbro- 
7. LOCUson CW, WAHLSTROM JL, ROCK DA et al.: A new class of CYP2C9 inhibitors: probing C9 specificity with high affinity benzbro- 

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

Sirs,

Polymyositis associated with human immuno- 

Letters to the Editor

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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, muscle fatigue, and progressive muscle weakness in his upper and lower limbs, but maximal in proximal muscles of the legs. Anti-retroviral 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/mm³, with a plasma viral load (HIV RNA) lower than 50 copies/mL. Physical examination showed diffuse 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 sharp 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 started. Six months later, the patient referred a remarkable improvement of muscle weakness and dysphagia. One year later, he was asymptomatic and electromyography 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

Multiple sclerosis and the antiphospholipid (Hughes) syndrome: A common 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