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A Benefit-Risk Assessment of Benzbromarone in the Treatment of Gout

Was its Withdrawal from the Market in the Best Interest of Patients?

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Abstract

Benzbromarone, a potent uricosuric drug, was introduced in the 1970s and was viewed as having few associated serious adverse reactions. It was registered in about 20 countries throughout Asia, South America and Europe. In 2003, the drug was withdrawn by Sanofi-Synthélabo, after reports of serious hepatotoxicity, although it is still marketed in several countries by other drug companies. The withdrawal has greatly limited its availability around the world, and increased difficulty in accessing it in other countries where it has never been available.

The overall aim of this paper is to determine if the withdrawal of benzbromarone was in the best interests of gouty patients and to present a benefit-risk assessment of benzbromarone. To determine this, we examined (i) the clinical benefits associated with benzbromarone treatment and compared them with the success of alternative therapies such as allopurinol and probenecid, particularly in patients with renal impairment; (ii) the attribution of the reported cases of hepatotoxicity to treatment with benzbromarone; (iii) the incidence of hepatotoxicity possibly due to benzbromarone; (iv) adverse reactions to allopurinol and probenecid. From these analyses, we present recommendations on the use of benzbromarone.

Large reductions in plasma urate concentrations in patients with hyperuricaemia are achieved with benzbromarone and most patients normalize their plasma urate. The half-life of benzbromarone is generally short (about 3 hours); however, a uricosuric metabolite, 6-hydroxybenzbromarone, has a much longer half-life (up to 30 hours) and is the major species responsible for the uricosuric activity of benzbromarone, although its metabolism by cytochrome P450 (CYP) 2C9 in the liver may vary between patients as a result of polymorphisms in this enzyme. It is effective in patients with moderate renal impairment. Standard dosages of benzbromarone (100 mg/day) tend to produce greater hypouricaemic effects than standard doses of allopourinol (300 mg/day) or probenecid (1000 mg/day).

Adverse effects associated with benzbromarone are relatively infrequent, but potentially severe. Four cases of benzbromarone-induced hepatotoxicity were identified from the literature. Eleven cases have been reported by Sanofi-Synthélabo, but details are not available in the public domain. Only one of the four published cases demonstrated a clear relationship between the drug and liver injury as demonstrated by rechallenge. The other three cases lacked incontrovertible evidence to support a diagnosis of benzbromarone-induced hepatotoxicity. If all the reported cases are assumed to be due to benzbromarone, the estimated risk of hepatotoxicity in Europe was approximately 1 in 17 000 patients but may be higher in Japan.

Benzbromarone is also an inhibitor of CYP2C9 and so may be involved in drug interactions with drugs dependent on this enzyme for clearance, such as warfarin. Alternative drugs to benzbromarone have significant adverse reactions. Allopurinol is associated with rare life-threatening hypersensitivity syndromes; the risk of these reactions is approximately 1 in 56 000. Rash occurs in approximately 2% of

patients taking allopurinol and usually leads to cessation of prescription of the drug. Probenecid has also been associated with life-threatening reactions in a very small number of case reports, but it frequently interacts with many renally excreted drugs. Febuxostat is a new xanthine oxidoreductase inhibitor, which is still in clinical trials, but abnormal liver function is the most commonly reported adverse reaction.

Even assuming a causal relationship between benzbromarone and hepatotoxicity in the identified cases, benefit-risk assessment based on total exposure to the drug does not support the decision by the drug company to withdraw benzbromarone from the market given the paucity of alternative options. It is likely that the risks of hepatotoxicity could be ameliorated by employing a graded dosage increase, together with regular monitoring of liver function. Determination of CYP2C9 status and consideration of potential interactions through inhibition of this enzyme should be considered. The case for wider and easier availability of benzbromarone for treating selected cases of gout is compelling, particularly for patients in whom allopurinol produces insufficient response or toxicity.

We conclude that the withdrawal of benzbromarone was not in the best interest of patients with gout.

Benzbromarone was selected for development from a number of benzofuran derivatives on the basis of its hypouricaemic efficacy in patients with gout.[1] It replaced benziodarone, a structurally similar uricosuric,[2] iodinated molecule that caused hypothyroidism.[3] Both benzbromarone and a major metabolite, 6-hydroxybenzbromarone (figure 1), are potent inhibitors of the renal tubular urate-anion exchanger, URAT1.[4,5] The half-life of benzbromarone is short (approximately 3 hours) but the active metabolite, 6-hydroxybenzbromarone,[6-8] a product of metabolism by cytochrome P450 (CYP) 2C9, has a much longer half-life (up to 30 hours)[7] and, because of its uricosuric activity and longer half-life, is probably the major active species during treatment with benzbromarone. Another major metabolite, 1′-hydroxybenzbromarone, is present in substantial concentrations in plasma, although its uricosuric activity has not been examined.

After almost 30 years of apparently safe use, with no reported severe adverse reactions, a case report of benzbromarone-induced hepatotoxicity was published in 1994[9] followed by several other reports of apparent hepatotoxicity.[10-12] This contributed to its eventual withdrawal from the market in 2003 by Sanofi-Synthélabo, whose formulation accounted for most of the European sales of the drug. However, it has been claimed that there was insufficient evidence or rationale to support this decision.[13] There has also been speculation that the primary driver for the withdrawal was that the company feared lawsuits.[13] Currently, benzbromarone is still marketed by other companies in some European countries, as well as in Japan, Brazil and several Asian countries (table I). It can be imported with difficulty into Australia and New Zealand.

Our goal was to carry out a benefit-risk assessment of benzbromarone to determine if its now limited availability is justified and is in the best interests of patients with gout. The aims of this assessment are as follows: (i) to evaluate the benefits of benzbromarone usage and to compare these with those of the alternative therapies; (ii) to evaluate the risks associated with benzbromarone by analysing the case-reports of hepatotoxicity; (iii) to assess the benefit-risk ratio of benzbromarone in clinical use; and (iv) to examine present recommendations on the use of benzbromarone. In comparisons of benzbromarone with other hypouricaemic drugs, we have included only those drugs for which the primary indication is the prophylactic treatment of gout. Other drugs with hypouricaemic effects,

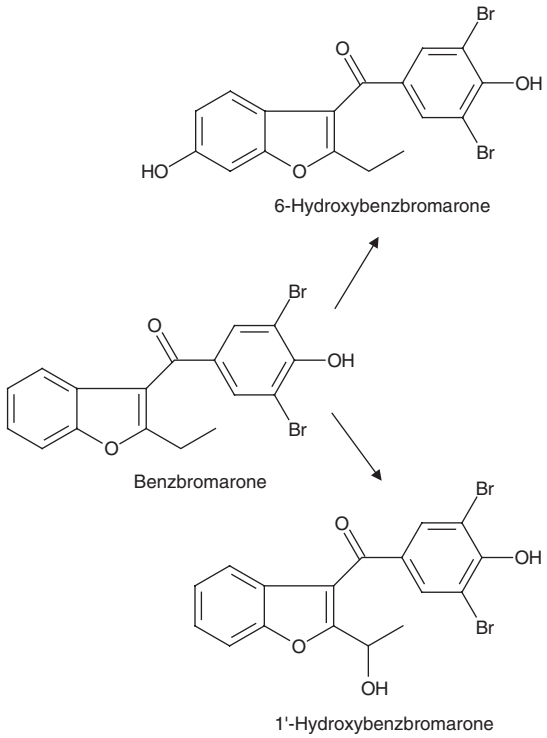

Fig. 1. Pathways of metabolism of benzbromarone. The principal metabolites are 6-hydroxybenzbromarone and 1′-hydroxybenzbromarone.[6-8] 5,6-Dihydroxybenzbromarone is produced from 6-hydroxybenzbromarone and is further oxidized in the presence of glutathione to yield conjugates that could be derived from the reactive quinone intermediate.[8] Another dihydroxy metabolite, 1′,6-dihydroxybenzbromarone (structure not shown) is also produced.

such as losartan and fenofibrate, have not been discussed.

1. Literature Searches

1.1 Benefits of Benzbromarone Treatment

The evidence for the benefit of benzbromarone in hyperuricaemic or gouty patients was evaluated using clinical trial data obtained by searching the Cochrane Central Register of Controlled Trials, PubMed, MEDLINE (1950–2007 week 35) and EMBASE (1988–2007 week 35). For PubMed, MEDLINE and EMBASE, the key words used were as follows: 'benzbromarone' and 'clinical trials', 'trials' and 'randomized clinical trials'. Papers outlining the effects of benzbromarone administered alone or in combination with other hypouricaemic drugs were examined. All papers describing the effects of benzbromarone (alone or in combination) on plasma urate in patients with gout or hyperuricaemia were included. Exclusion criteria were as follows: papers describing only changes in the number of acute attacks of gout; papers in which plasma urate was not measured; and studies on the prophylactic use of benzbromarone during cytotoxic therapy. Studies in healthy subjects were included in an examination of the pharmacology of benzbromarone but have been excluded from tabulated data on its hypouricaemic activity (table II). Papers were included irrespective of language. It was not necessary to eliminate any studies because of poor quality. The product information for benzbromarone was obtained from Torii Pharmaceutical Co., Tokyo, Japan (available from the authors).

1.2 Risks of Benzbromarone Treatment

A comprehensive literature search was conducted using the keywords 'benzbromarone', 'hepatotoxicity', 'acute liver failure' and 'fulminant hepatitis' in various databases including MEDLINE, PreMedline and EMBASE, using the dates and search terms described in the previous section. Papers were included irrespective of language. The Google search engine was also used to identify commercial and authoritative documents on benzbromarone hepatotoxicity and on its withdrawal from the market. A similar search using this search engine on any other adverse reactions associated with benzbromarone found no results.

2. Epidemiology and Burden of Gout

The economic cost of gout is considerable because of its high prevalence.[35] Highly variable figures for the prevalence of gout have been recorded with most reported values in the UK and US being in the range of 1.4–3.4%.[36,37] Reported values on the annual incidence of gout are also variable but there is general agreement that the incidence is increasing.[36,38] There has been little study of the economic burden of gout and on the disability-

Table I. Current availability of benzbromarone in various countries

Country	Company	Marketing status[a]	Trade name[b]
Argentina	Labinca	Withdrawn	Max Uric[c]
Austria	Ana	Available	Allobenz[c]
Austria	Viatris	Available	Duovitan[c]
Austria	Gerot	Available	Gichtex Plus[c]
Austria	Sanofi-Synthélabo	Withdrawn	Uricovac
Austria	Kwizda	Withdrawn	Uroplus
Belgium	Therabel	Available	Comburic[c]
Belgium	Sanofi-Synthélabo	Withdrawn	Desuric
Brazil	Evolabis	Available	Narcaricina
France	Inava	Withdrawn	Anurate
France	Sanofi Winthrop	Withdrawn	Desatura
France	Sanofi-Synthélabo	Withdrawn	Desuric
Germany	Azupharma	Withdrawn	Azubromaron
Germany	Henning	Withdrawn	Acifugan
Germany	Ratiopharm	Available	Allo. Comp.[c]
Germany	Aventis	Withdrawn	Allomaron[c]
Germany	Merz	Withdrawn	Harolan
Germany	Merz	Available	Harpagin
Germany	Heumann	Withdrawn	Narcaricin
Germany	Labaz	Withdrawn	Uricovac
Germany	Sanofi Winthrop	Withdrawn	Uricovac Comp[c]
Hong Kong	Heumann	Withdrawn	Narcaricin
Hungary	Merz	Available	Harpagin
Italy	IRBI	Withdrawn	Urifugan[c]
Japan	Torii	Available	Urinorm
Malaysia	Merz	Withdrawn	Harpagin
Mexico	Sanfer	Withdrawn	Desuric
Netherlands	OTL	Available	Desuric
Portugal	Jaba	Withdrawn	Acifugan[c]
Singapore	Ludwig	Withdrawn	Narcaricin
South Africa	Aventis	Withdrawn	Allomaron
South Africa	Sanofi-Synthélabo	Withdrawn	Minuric
Spain	Lacer	Withdrawn	Acifugan[c]
Spain	Fides Ecopharma	Withdrawn	Facilit[c]
Spain	OTL	Available	Urinorm
Switzerland	Synthelabo	Withdrawn	Acifugan[c]
Switzerland	Sanofi-Synthélabo	Withdrawn	Desuric
Switzerland	Mepha	Withdrawn	Obaron
Thailand	Aventis	Withdrawn	Allomaron[c]
Thailand	Heumann	Withdrawn	Narcaricin

a As per Martindale complete drug reference.[14] The list is verified and edited following confirmation with various pharmaceutical companies.

b The use of trade names is for identification purposes only and does not imply endorsement.

c Combination preparation, consisting of allopurinol 100 mg and benzbromarone 20 mg.

adjusted life-years associated with this disease. Costs of therapy for new cases of gout in men have been estimated at approximately $US27 million per year in the USA.[39] However, this estimate does not

Table II. Clinical trials of benzbromarone in patients with hyperuricaemia and/or gout

Study	Treatment comparison	Benzbromarone dosage (mg/day)	Trial type	No. of patients	Trial period	Mean reduction in plasma urate (%)[a]
Nakamura[15]	Baseline	100	RCT	20	7 d	0 vs 46
de Gery et al.[16]	Baseline	25–100	CT	50	Several y	0 vs 48
Ravera[17]	Baseline[b]	100–200	CT	6	10–12 d	0 vs 36
Didier and Olmer[18]	Baseline[b]	100	CT	43	24 wk	0 vs 54
Ferber et al.[19]	Baseline	50–100	CT	1984	8 wk	0 vs 35
Bluestone et al.[20]	Baseline	40–80	CT	381	Up to 2 y	0 vs 34
Scott[21]	Baseline	100	CT	22	Up to 5 mo	0 vs 55
Zurcher et al.[22]	Baseline[b]	100	CT	25	4 wk	0 vs 46
Nakamura[23]	Allopurinol 200 mg/day	100	RCT	20	7 d	37 vs 34
Mertz[24]	Allopurinol 300 mg/day	50	CCT	28	7 d	36 vs 47
Schepers[25]	Allopurinol 300 mg/day	100	CCT	6	7 d	24 vs 52
Perez-Ruiz et al.[26]	Allopurinol 300 mg/day	100	CCT	86	1 y	34 vs 58
Perez-Ruiz et al.[27]	Allopurinol 100–300 mg/day[b]	100–200	RCT	36	9–24 mo	33 vs 56
Hanvivadhanakul et al.[28]	Allopurinol 300 mg/day	100	CCT	14	4 wk	44 vs 58
Schepers[25]	Probenecid 1000 mg/day	100	RCT	6	1 wk	2 vs 52
Liang et al.[29]	Probenecid 1500 mg/day	50	RCT	74	12 wk	32 vs 40
Mertz[30]	Allopurinol 300 mg/day	Comb	CCT	24	9 d	33 vs 39
Frerick et al.[31]	Allopurinol 300 mg/day	Comb	RCT	80	36 wk	40 vs 40
Berg[32]	Allopurinol 300 mg/day	Comb	RCT	60	24 wk	20 vs 27
Akkasilpa et al.[33]	Allopurinol 300 mg/day	Comb	CCT	94	4 wk	39 vs 26
Arntz et al.[34]	Benzbromarone 20 mg/day	Comb	RCT	12	4 wk	19 vs 35
Arntz et al.[34]	Allopurinol 100 mg/day	Comb	RCT	12	4 wk	21 vs 35

a Effect of comparator drug vs effect of benzbromarone.

b Trials conducted in patients with renal impairment, creatinine clearance ranges from 20 to 80 mL/min.

CCT = controlled clinical trial; **Comb** = combination; **CT** = clinical trial (within person comparison); **NA** = not assessed; **RCT** = randomized controlled trial.

include continuing costs of patients with chronic gout, non-therapy costs nor data on females, who represent about 10% of people experiencing gout.

3. Treatment Strategies for Gout

3.1 Purpose of Treatment

Urate is the end product of purine metabolism in humans. Excessive plasma urate concentrations may be a result of excessive production or impaired elimination of uric acid. In some predisposed individuals, hyperuricaemia leads to precipitation of monosodium urate, notably in synovial joints, where it may elicit acute inflammation, which is clinically manifested as gouty arthritis. Acute attacks of gouty arthritis are extremely painful but can be treated effectively. Furthermore, the acute attacks are usually self-limiting with symptoms subsiding in about a week. However, long-term poorly treated gout may lead to tophaceous gout, which causes destruction and deformation of joints. Hence, to reduce the suffering associated with repeated acute attacks, as well as to prevent the detrimental consequences of gout, long-term preventative treatment is warranted.

3.2 Current Therapies and Outcomes

The current strategy for gout management is, firstly, to treat the acute attack and then to lower excessive uric acid stores and prevent recurrent attacks by reducing the concentrations of plasma urate. Decreased plasma levels of urate correlate with a reduced number of gout attacks and urate concentrations are therefore widely accepted as the surrogate marker to measure and evaluate treatment.

It is common practice to recommend that patients adopt a low purine diet although the hypouricaemic effect of diet alone appears small[40] and is often rejected by patients.[41] Acute gout is often associated with excessive intake of alcohol and restricted alcohol use is often suggested. However, this suggestion is commonly ignored, obviously preventing any effect of reduced alcohol *per se* and decreasing the success of long-term treatment with allopurinol.[42]

There are few randomized controlled trials of good quality on the pharmacological treatment of gout, especially on the prevention of recurrent gout.[43] This is because of the lack of new treatments and the absence of clinical trials of the quality required to give confidence in proposed therapeutic approaches.[44] Current guidelines rely more on clinical experience rather than on well controlled clinical trials.

In an acute attack of gout, pharmacological therapies include NSAIDs, colchicine or corticosteroids. For the prevention of recurrent attacks, urate-lowering therapy is generally required. Treatments include the xanthine oxidoreductase inhibitors allopurinol and febuxostat, if it becomes available, uricosuric agents, such as probenecid, and, if available, sulfinpyrazone or benzbromarone, and the uricolytic agent, urate oxidase. Prophylactic pharmacotherapy is not recommended in hyperuricaemic patients with no history of gout, as most patients with hyperuricaemia do not develop gout.[45] Furthermore, treatment with allopurinol carries a risk of rare, but serious, hypersensitivity which, in turn, carries a high mortality rate, discussed in more detail in section 6.6.1.[46] However, short-term hypouricaemic therapy is reasonable if plasma urate concentrations are well above the upper limit of normal and if this elevation occurs suddenly or for a short period of time, as is likely, for example, following therapy with cytotoxic drugs.

At a frequency of more than two acute attacks per year, it is cost effective to start long-term, urate-lowering therapy.[47] The uricosuric agent probenecid was introduced as a hypouricaemic drug in 1951 but was largely superseded by allopurinol, which became available in 1961. Allopurinol owes its popularity to its once-daily dosage regimen, good efficacy even in patients with substantial renal impairment and, unlike the uricosuric agents, the lack of need to maintain a high urinary output or alkalinization of urine. It has also been suggested that allopurinol reduces the plasma concentrations of urate more rapidly and to a greater extent than probenecid.[21] Allopurinol also decreases urinary urate levels and is useful in patients with recurrent renal stones. For these reasons, the recommended first-line drug for prevention of gout is allopurinol.[48] About 80% of patients achieve plasma urate concentrations below the sodium urate saturation level of 0.42 mmol/L with allopurinol.[49,50] However, a lower target level of plasma urate <0.36 mmol/L,[48] or even 0.30 mmol/L,[51] has been recommended to achieve resolution of tophi and therefore 'cure' gout, but many patients do not achieve these lower targets despite high plasma concentrations of oxypurinol, the active metabolite of allopurinol.[49,50,52]

Several factors may limit the activity of allopurinol. Firstly, with higher pre-treatment levels of plasma urate, there is less chance that a standard dose of allopurinol (300 mg/day) will reduce plasma urate concentrations to <0.36 mmol/L.[27,53] Secondly, allopurinol may decrease the renal clearance of urate. Two groups have reported that urate clearance decreased during allopurinol treatment,[54,55] although another group found no change.[26] Diuretics are commonly taken by gouty patients because of common comorbidities but they decrease the hypouricaemic efficacy of allopurinol.[27]

A further obstacle in achieving a satisfactory hypouricaemic effect is renal impairment, a common co-morbidity in patients with gout.[56] Although allopurinol is useful in patients with renal impairment, its use in these patients still presents a clinical challenge, since the active metabolite of allopurinol, oxypurinol, is excreted renally and is therefore retained in patients with renal impairment. This may be associated with an increased risk of serious hypersensitivity reactions.[57] Therefore, adjusting allopurinol dose according to renal function is recom-

mended,[57] but the recommended dosage schedule may be inadequate in the control of hyperuricaemia.[49,52] Alternative or additional pharmacotherapies in such patients thus becomes an important consideration.

Before Sanofi-Synthélabo withdrew its product in Europe, benzbromarone was widely used because of its once-daily dosage regimen, efficacy in moderate renal impairment and because it had relatively few adverse effects.[13]

4. Pharmacology of Benzbromarone

4.1 Pharmacokinetics

Benzbromarone is largely protein-bound in serum (99%),[58] and the half-life is approximately 3 hours.[59] However, the prolonged uricosuric action[59] can be correlated with the much longer half-life of elimination of its uricosuric metabolite, 6-hydroxybenzbromarone. Most of the parent drug and its metabolites are excreted in bile and faeces, and only 6% of the drug is excreted renally.[60] The liver is the main site of metabolism of benzbromarone, with CYP2C9 being the principal enzyme involved.[61] Individuals with normal liver function but with a prolonged benzbromarone half-life, much greater plasma concentrations of 1′-hydroxybenzbromarone and impaired formation of 6-hydroxybenzbromarone have been identified.[7] Subsequent work has detected individuals homozygous for a variant of the CYP2C9 enzyme, CYP2C9*3, in which isoleucine is substituted for leucine. These individuals have increased plasma concentrations of benzbromarone and a decreased ratio of 6-hydroxybenzbromarone to benzbromarone[62] but any relationship between this CYP2C9 variant and the hepatotoxicity or hypouricaemic activity of benzbromarone is unknown. Other inherited substitutions in CYP2C9 are known;[63] however, again, their influence on the toxicity or efficacy of benzbromarone is not known. Although the major metabolism of benzbromarone is hepatic, dosage adjustments are not required in patients with moderate cirrhosis.[64]

4.2 Pharmacodynamics

The effects of benzbromarone on individual transporters of urate have been less well studied than those of probenecid. In rats, benzbromarone reduces uric acid reabsorption when injected in the proximal but not distal tubules of the kidney[65] and, as anticipated from its uricosuric effect, benzbromarone inhibits the urate transporter URAT1; 50 μmol/L of benzbromarone inhibited 93% of uric acid uptake by the transporter *in vitro*.[4] The concentrations of benzbromarone and, more importantly, the concentrations of the active metabolite, 6-hydroxybenzbromarone, in the proximal tubule are, however, unknown.

In addition to its resorption by URAT1, urate is secreted in the kidney by two organic ion transporters, OAT1 and OAT3.[66] Inhibition of these processes by probenecid tends to reduce its uricosuric effect. Both probenecid and benzbromarone inhibit OAT1;[67] however, benzbromarone does not influence the pharmacokinetics of penicillins.[68,69] Benzylpenicillin is secreted principally by OAT3,[66] suggesting that benzbromarone is not an inhibitor of OAT3. Overall, benzbromarone may be a more selective inhibitor of urate transporters than probenecid.

The greater selectivity may explain an early observation in the rabbit kidney *in vitro*, namely that benzbromarone shows a steeper relationship between concentration and inhibition of urate uptake than is shown by either probenecid or sulfinpyrazone.[70] If this contrast can be extrapolated to the therapeutic effects of these compounds, one would expect to see a greater increase in hypouricaemic activity with relative increases of dosage of benzbromarone than with probenecid or sulfinpyrazone.

In normal or hyperuricaemic subjects, benzbromarone increases urinary urate excretion shortly after an oral dose of this drug. Acutely, the clearance of urate is increased by over 500%.[71] The increased renal clearance of urate leads to a mean reduction in plasma urate of between 25% and 50%, during long-term therapy (table II). The percentage decrease in plasma urate appears to be unrelated to initial urate

concentrations, i.e. during administration of a fixed dose of benzbromarone, the percentage decline in plasma concentrations of urate is relatively consistent irrespective of the initial concentrations.[15,16,20,21] Thus, satisfactory concentrations appear more difficult to achieve with higher pre-treatment plasma concentrations of urate and the optimal hypouricaemic response may be produced by the gradual increase in dosage.[27]

As expected from any marked reduction in the plasma concentrations of urate, long-term treatment with benzbromarone reduces the frequency of acute attacks of gout. For benzbromarone, the number of acute attacks was reduced by 35–100% after 2 years of treatment.[20,27,72] Reduction in plasma urate also increases the rate of reduction of the size of tophi.[73] In this regard, benzbromarone and allopurinol "are equally effective when optimal serum urate levels are achieved".[73]

4.3 Benzbromarone in Patients with Renal Impairment

Unlike probenecid (section 5.3), significant hypouricaemic activity of benzbromarone is retained in patients with substantially impaired renal function.[17,18,72,74] The hypouricaemic response to benzbromarone may be decreased somewhat[65,74] but a dosage increase to 150–200 mg/day improves the hypouricaemic response in patients with creatinine clearances (CL_{CR}) in the range 20–40 mL/min.[27] Benzbromarone also shows good hypouricaemic activity in patients with renal transplants provided that their CL_{CR} is greater than about 25 mL/min.[22]

5. Comparison of the Benefits of Benzbromarone with Other Therapies

5.1 Allopurinol

At standard doses (100 mg/day), the hypouricaemic activity of benzbromarone is somewhat more efficacious than that of allopurinol (300 mg/day; table II). However, the effect of allopurinol can be increased in many patients with normal or only slightly impaired renal function if the dose of allopurinol is increased to 450–600 mg/day.[26] By contrast, the dosage of benzbromarone can be reduced to below 100 mg/day in many patients and the plasma urate concentrations still remain below 0.36 mmol/L.[26]

When patients are treated according to their uric acid excretion status, benzbromarone may be more effective than allopurinol in patients who underexcrete uric acid. In a parallel study, 80 patients were assigned to either benzbromarone ('under-excretors') or allopurinol (either 'normo-excretors' or 'under-excretors') based on their 24-hour urine uric acid production.[26] Benzbromarone showed greater efficacy in reducing plasma urate concentrations in under-excretors when compared with either groups using allopurinol (58% vs 33%); the 'under-excretors' represent at least 80% of patients with gout.[75]

5.2 Combination of Allopurinol and Benzbromarone

The combination of benzbromarone (60 mg/day) and allopurinol (300 mg/day) produces a greater hypouricaemic response than allopurinol alone.[73,76] Perez Ruiz et al.[73] also found a good hypouricaemic response with the combination of benzbromarone (50 mg/day) and allopurinol (300 mg/day). In the latter study, monotherapy with benzbromarone produced a similar hypouricaemic response, although the dose of benzbromarone was higher (75–150 mg/day). As discussed above (section 4.2), benzbromarone reduces the number of acute attacks of gout and, in a very thorough study in six patients, additional treatment with benzbromarone decreased the number of acute attacks in patients who had not responded satisfactorily to allopurinol.[72]

A low-dose combination of allopurinol (100 mg) and benzbromarone (20 mg) has been introduced with the aim of lowering the dosage of both drugs. In gouty patients, this combination produces greater hypouricaemic effects than either drug alone at low doses (table II).[34] However, the low-dose combination produces a lesser effect than benzbromarone alone at a full dose (100 mg).[30] Similar trends are seen in healthy subjects.[77,78] This low-dose combination has also been compared with the standard

dose of allopurinol (300 mg/day) but there are conflicting data on the comparative effects on plasma urate levels; the low-dose combination has been reported to be superior, inferior and similar to allopurinol 300 mg/day (table II). [30-33] The combination therapy may be an option in patients with moderate renal impairment in order to minimize the risk of hypersensitivity to allopurinol and benzbromarone.

As is the case with probenecid, benzbromarone increases the renal clearance of oxypurinol in healthy subjects,[77,79] but there is doubt about the interaction in hyperuricaemic patients because of one report in which it was recorded that a 60-mg dose of benzbromarone did not decrease the plasma concentrations of oxypurinol in patients with normal renal function.[76] The lowered plasma urate is still produced, however, irrespective of the reported effect of benzbromarone on oxypurinol clearance.

5.3 Probenecid

The hypouricaemic efficacy of benzbromarone is comparable to that of probenecid. In the only randomized controlled trial on the two uricosuric drugs, each produced similar reductions in the plasma concentrations of urate (benzbromarone 50 mg vs probenecid 1500 mg/day; table II).[29] In older reports on probenecid, it was noted that probenecid generally showed a lesser hypouricaemic effect in patients with substantial renal impairment.[80,81] The response of the patients with impaired renal function was stated to be moderate and attacks of acute gout persisted.[81] However, as far as we are aware, there is no proven CL_{CR} level below which probenecid may be expected to have a clinically insignificant hypouricaemic effect, although it is widely claimed that probenecid has a lesser hypouricaemic effect than benzbromarone in renally impaired patients. As noted above, the hypouricaemic activity of benzbromarone in patients with substantial renal impairment is increased if the dose is increased. We have found no similar study in which the dose of probenecid was increased in renal impairment. Possibly, the selectivity of benzbromarone makes it a more efficacious uricosuric drug in renal impairment, but further clinical studies are required.

5.4 Combination of Allopurinol and Probenecid

In an early study, it was found that the addition of probenecid increased the hypouricaemic effect only by about 10%.[82] Most of the patients had considerable renal impairment, which limits the effect of probenecid alone. By contrast, in a trial in which patients had CL_{CR} >50 mL/min, the addition of probenecid 1000 mg/day to allopurinol 200–300 mg, effectively normalized plasma urate concentrations in 83% of patients who were refractory to allopurinol treatment alone. This effect was not significantly different from that of benzbromarone, which was used in the same cohort before its withdrawal.[83] This study shows that allopurinol-probenecid combination therapy is equivalent to benzbromarone in efficacy and may be used as another viable alternative to monotherapy with allopurinol or benzbromarone, provided that the patient's renal function is normal or only moderately impaired.

The effects of probenecid on the renal clearances of oxypurinol and urate are generally consistent with those of benzbromarone. In healthy subjects, probenecid increases the renal clearance of oxypurinol with a consequent reduction in the steady state plasma concentrations of oxypurinol.[79,84] However, the direct uricosuric effect of probenecid more than overcomes the effect of the lower plasma concentrations of oxypurinol and the plasma concentrations of urate are nearly 50% lower than during dosage with allopurinol alone.[84]

5.5 Sulfinpyrazone

Sulfinpyrazone is a uricosuric agent that has been removed from the market by the major supplier, Novartis, in many countries; however, it is still available in Canada, Italy, Portugal, the US and the UK. It is structurally similar to phenylbutazone and, like phenylbutazone and other NSAIDs, inhibits the synthesis of prostaglandins and related compounds, such as thromboxane A2 and prostacyclin. Consis-

tent with its inhibition of the synthesis of thromboxane A2, sulfinpyrazone decreases the aggregation of platelets but its clinical activity appears slight, and inferior to that of aspirin (acetylsalicylic acid).[85,86]

The hypouricaemic action of allopurinol can be increased by the addition of sulfinpyrazone but, similar to probenecid, the addition of sulfinpyrazone is expected to have a lesser effect in patients with renal impairment.[82,87]

5.6 Febuxostat

Febuxostat is a promising novel selective xanthine oxidase inhibitor that is currently in phase III trials.[88] It has not been compared directly with benzbromarone, although it has been shown to have similar efficacy to allopurinol 300 mg/day.[89]

6. Risk Evaluation of Benzbromarone

6.1 *In Vitro* and Animal Studies

The laboratory evidence for benzbromarone causing hepatotoxicity is not strong. Since both benzarone and amiodarone have established hepatotoxicity profiles and are structurally related to benzbromarone, they may share the same mechanism of hepatotoxicity as benzbromarone.[9] Mitochondrial toxicity induced by amiodarone and benzarone has been replicated with benzbromarone in rat hepatocytes.[90] Furthermore, a series of toxicological studies[91-93] demonstrated proliferation of peroxisomes, a mechanism associated with carcinogenesis, in the livers of rats administered benzbromarone. However, the same effect could not be demonstrated in human hepatocytes. The peroxisome proliferation property of benzbromarone in rat hepatocytes was further investigated. Benzbromarone is a ligand of peroxisome proliferator-activated receptor (PPAR)-α but not of PPAR-γ.[61] PPAR-γ is associated with apoptosis and this is thought to be the mechanism of troglitazone-induced fulminant hepatitis.

A minor metabolite of benzbromarone, 5,6-dihydroxybenzbromarone (figure 1), is potentially toxic.[6-8] In the presence of glutathione, this metabolite is further oxidized by CYP2C9 to yield glutathione conjugates that could be derived from a reactive quinone intermediate.[8] A similar reaction with hepatic proteins could be directly hepatotoxic. Alternatively, reaction of the quinone metabolite could lead to the formation of antigenic protein adducts in the liver and the several other tissues in which CYP2C9 is expressed.[94] This is more likely than direct hepatotoxicity, considering the rarity of benzobromarone-induced hepatotoxicity.

6.2 Adverse Reactions Reported in Clinical Trials

Most clinical trials of benzbromarone have reported few or no adverse reactions and there have been no reports of overdose. Discontinuation of treatment due to intolerance has usually been because of diarrhoea and was reported in 3–4% of patients.[74] Other rare adverse reactions such as temporary impotence, allergic conjunctivitis and severe skin rash were also reported, but only in sporadic cases.[65] It was reported in the product information for benzbromarone (Torii Pharmaceutical Co.) that over 0.1% of the patients in clinical trials had "elevated liver enzymes" but no cases of jaundice were reported. No complications occurred in eight patients with liver cirrhosis receiving benzbromarone treatment.[64] However, given the infrequent and idiosyncratic nature of the cases of hepatotoxicity, tolerance in this small group is not unexpected. Benzbromarone, in addition to being metabolized by CYP2C9, is also an inhibitor of that enzyme, and therefore potentiates the effect of warfarin.[95] The genetic polymorphism in the CYP2C9 enzyme has been reported in individuals with leflunomide-induced hepatotoxicities[96] and speculated as a risk factor in several other drugs that are substrates of CYP2C9.[97] This may explain the idiosyncratic hepatotoxicity related to benzbromarone, although confirmation with case- control studies is needed.

Acute gout attacks are common adverse effects during the initiation of any urate-lowering therapy and have also been reported with benzbromarone.[74] In order to prevent acute gout with hypouricaemic

drugs, it is widely recommended that all such drugs should be introduced gradually, starting at low doses and with initial concomitant administration of NSAIDs or low-dose colchicine. A particular problem with all uricosurics, including benzbromarone, is nephrolithiasis, which is managed either by the maintenance of a high urinary output and/or alkalinization of urine. However, nephrolithiasis may still occur, often because of a lack of compliance with these recommendations.[74]

As discussed earlier, benzbromarone appears to have greater selectivity for urate transporters than probenecid. Consequently, benzbromarone may not produce some of the adverse renal effects produced by probenecid because of probenecid's inhibition of OAT3. An example is the decreased excretion of methotrexate when administered concomitantly with probenecid, an interaction that requires decreased dosage of methotrexate.[98] However, more direct examination of possible renal interactions of benzbromarone is required.

6.3 Spontaneous Reports of Hepatotoxicity in the Literature

Four reports of benzbromarone-related hepatotoxicity were retrieved (table III).[9-12] One patient was from the Netherlands and three from Japan. The Dutch patient survived but two of the three Japanese patients died. Several important documents on the withdrawal of benzbromarone, including the press release from the French Health Products Safety Agency,[99] the WHO pharmaceuticals newsletters[100] and a commentary letter were also retrieved.[13] The Periodic Safety Update Report (PSUR) listed 11 patients who developed hepatotoxicity from benzbromarone.[101] We assume that the four published case histories are included in the number. It is stated that more than half the patients were Japanese and we have further assumed that the remaining five patients were European. Unfortunately, we failed to obtain any further details from the European Medicines Agency or Sanofi-Synthélabo. Of the reported total of 11 patients, 9 died. Figure 2 shows the marketing and withdrawal timeline of benzbromarone. The drug was registered 30 years ago and, therefore, was well past its patent protection period at the time of withdrawal by Sanofi-Synthélabo.

6.4 Qualitative Assessment

We applied a set of clinical guidelines for evaluating drug-related hepatotoxicity, developed by Navarro and Senior,[103] to examine the quality of evidence in support of the proposition of benzbromarone-caused hepatotoxicity from the retrieved reports (table III). In summary:

- The three Japanese patients had no history of hepatic disease.[10-12] The Dutch patient had no evidence of chronic hepatic impairment but she had been jaundiced at 22 years of age, 46 years before the acute episode attributed to benzbromarone.[9]
- Other possible causes of liver failure, such as viral hepatitis or autoimmune diseases, were excluded.
- Other drugs, including alcohol, can probably be excluded as causes of the hepatotoxicity. Excessive intake of alcohol was not recorded in any of the four patients with hepatotoxicity. One patient was taking methyldopa (table III), which can cause liver impairment. However, this patient was rechallenged with benzbromarone resulting in mildly elevated liver enzymes. This makes it probable that benzbromarone caused the hepatotoxicity, not the methyldopa.
- All patients also showed improvement either clinically or with respect to liver function tests after cessation of benzbromarone, although other drugs were also ceased.
- The lymphocyte stimulation test was performed in three patients but only one case was positive. However, the test was performed only using benzbromarone, not the metabolites that are present in high concentrations in plasma or the potentially toxic metabolite, 5,6-dihydroxybenzbromarone.
- Liver biopsy in three patients showed histopathology consistent with fulminant hepatic necrosis. Liver function tests in all patients showed a

Table III. Published cases of hepatotoxicity due to benzbromarone

Case description	Temporal relationship (time taken from initiation of treatment to onset of clinical liver disease)	Exclusion of other causes	Patient's condition improves after stopping benzbromarone?	Outcome	Comments	Reference
68-y-old female with chronic gout refractory to allopurinol treatment was initiated on benzbromarone 100 mg/day	3 mo after initial exposure, patient presented with "influenza-like" complaints, diarrhoea and dark urine. Laboratory data showed AST 509 U/L, ALT 793 U/L, γGT 145 U/L and AP 217 U/L. 6-wk post rechallenge with benzbromarone 25–50 mg/day 2 y later resulted in mildly deranged liver function (AST 139 U/L, ALT 199U/L, γGT 34 U/L, AP 102 U/L) but without clinical symptoms	Negative for HBsAg, anti-HBsAb, anti-HBc and HAV Igs. Antinuclear, antimitochondrial and anti-smooth muscle antibodies were also absent. U/S and ERCP showed no bile duct diseases. Hepatitis C was not ruled out. Patient was also on methyldopa for hypertension, which can cause liver impairment	Yes; symptoms improved and LFT normalized. LFT normalized again after withdrawal of the second benzbromarone challenge	After the second challenge, liver injury did not recur as severely onset was quicker. The gout had since been managed with colchicine, allopurinol and sulfinpyrazone without problems. Methyldopa use continued throughout	First report of benzbromarone related hepatotoxicity after 20 y of its availability. Patient reportedly had a history of "jaundice" at 22 y of age, no diagnosis was given	9
62-y-old male treated for hyperuricaemia	5 mo after initiation of benzbromarone 75 mg/day, patient was admitted to hospital for "liver dysfunction" with AST 1369 U/L	Serological tests of HAV to HGV tests were all negative. Antinuclear antibody was low-titre positive. LST for benzbromarone was negative. Other causes of hepatitis were reportedly excluded but no details were given. Concomitant medications were not reported	No; clinical condition continued to deteriorate. ALT level dropped but the PT and total bilirubin continued to rise despite benzbromarone withdrawal	Patient died from liver failure on the 62nd day of admission despite intensive support care including bilirubin absorption treatment	First case of mortality. Autopsy showed severely atrophic liver (690 g) and massive hepatic cell necrosis consistent with acute fulminant hepatic failure	10

Continued next page

Table III. Contd

Case description	Temporal relationship (time taken from initiation of treatment to onset of clinical liver disease)	Exclusion of other causes	Patient's condition improves after stopping benzbromarone?	Outcome	Comments	Reference
58-y-old male treated for hyperuricaemia	After 7 mo of benzbromarone, unstated dose, patient developed mild fever, malaise, anorexia, dark urine, pruritus and jaundice. Total bilirubin 135 mg/L, AST 736 IU/L, ALT 1168 IU/L, AP 792 IU/L and γGT 1102 IU/L	Other causes were excluded: HBsAb positive but all other hepatitis "virus markers" were negative. LST for benzbromarone was negative. Concomitant medications include allopurinol, tocopherol, niacin, alprazolam, theophylline, azelastine and nilvadipine	No; clinical condition continued to deteriorate with persistence of jaundice, development of hepatic encephalopathy and increased PT and total bilirubin. ALT improved after stopping benzbromarone	Prednisolone 30 mg/day treatment plus plasma exchange and haemodiafiltration was commenced after persistent hepatic failure. CT of abdomen at the time showed right lobe mild atrophy 1 y later CT showed left lobe hypertrophy and macro-nodular changes in the right lobe	Biopsy and Masson-trichrome staining of the liver at recovery showed fibrosis, bile duct-like structure, aggregation of lymphocytes and hepatocytes. There was also nuclear enlargement seen in some hepatocytes	11
53-y-old female treated for hyperuricaemia	Benzbromarone 100 mg/day was co-administered with allopurinol for 2 mo. Patient developed diarrhoea, nausea, loss of appetite, severe fatigue and jaundice. Laboratory: albumin 2.5 g/dL, AST 3090 U/L, ALT 1140 U/L, LDH 945 U/L, AP 123 U/L, total bilirubin 233 mg/L, direct bilirubin 137 mg/L, creatinine 26 mg/L, NH_3 160.6 μg/dL, PT 26.5 s	Other causes excluded: past but no current HBV infection. HAV, HCV, EBV and CMV were all negative. Relevant autoantibodies were all negative. LST was positive for benzbromarone. Concomitant medication included dipyridamole, cisapride and alfacalcidol for several years	No; although AST and ALT dropped dramatically after benzbromarone withdrawal, the physical and mental state of the patient deteriorated consistent with fulminant hepatic failure	Living-related liver transplantation undertaken after failure of continuous haemodiafiltration and plasma exchange to improve her liver function. Patient died from sepsis 3 mo after the transplantation	Biopsy of the original liver showed massive necrosis consistent with fulminant hepatitis. Centrilobular necrosis pattern. Mild inflammatory cell infiltrate was seen	12

Anti-HBc = hepatitis B core; **AP** = alkaline phosphatase; **CMV** = cytomegalovirus; **CT** = computed tomography; **EBV** = Epstein-Barr virus; **ERCP** = endoscopic retrograde cholangiopancreatography; **GT** = glutamyl transpepticlase; **HAV** = hepatitis A virus; **HBsAb** = hepatitis B virus surface antibody; **HBsAg** = hepatitis B virus surface antigen; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HGV** = hepatitis G virus; **Igs** = immunoglobulins; **LDH** = lactate dehydrogenase; **LFT** = liver function test; **LST** = lymphocyte stimulation test; **PT** = prothrombin time; **U/S** = ultrasonography.

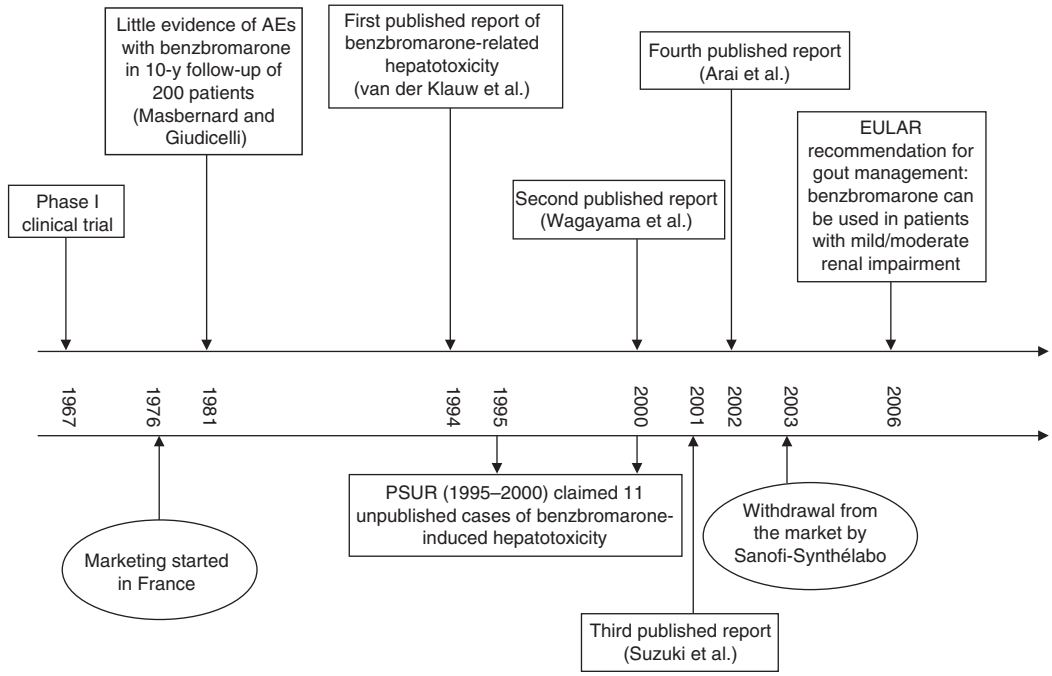

Fig. 2. Timeline of introduction and withdrawal of benzbromarone. **AE** = adverse effects; **EULAR** = European Union League Against Rheumatism;[48] **PSUR** = Periodic Safety Update Report.[99] Key publications: Arai et al.,[12] Masbernard and Giudicelli,[102] Suzuki et al.,[11] van der Klauw,[9] and Wagayama et al.[10]

predominantly hepatocellular pattern of hepatotoxicity.

In addition, it is notable that benzbromarone was apparently used for asymptomatic hyperuricaemia in three of the four patients (table III). This is inappropriate as it has been recommended for many years that hypouricaemic therapy should be used only for lowering plasma urate in patients with recurrent acute or chronic gout or where marked elevation of plasma urate may occur during cytotoxic therapy. Furthermore, it was stated that one patient did not respond to therapy with allopurinol, possibly indicating that this patient may have used allopurinol inappropriately or complied poorly with the prescribed dose.

6.5 Quantitative Assessment

A crude indication for the incidence of benzobromarone-induced hepatotoxicity comes from the number of European cases in the 6-year period between 1995 and 2000, inclusive. As discussed in section 6.3, it is assumed that five cases of fulminant hepatitis occurred in Europe. The number of prescriptions for benzbromarone is difficult to estimate. In the report released by French Health Products Safety Agency,[101] about 56 000 prescriptions each year were issued in France and the Netherlands before the withdrawal of benzbromarone. The total population of European countries in which benzbromarone was available (table I) was 301 million compared with 78 million in France and the Netherlands. Assuming the prescription pattern is similar across Europe where benzbromarone was generally available,[104] approximately 216 000 ($56\,000 \times 301 \times 10^6/78 \times 10^6$) prescriptions per year may be estimated for benzbromarone in Europe, including France. Assuming 100% compliance, that benzbromarone was taken once daily and 30 tablets are contained in one prescription (packet), then 12 prescriptions are required by each patient each year. It follows that 18 000 (216 000/12) patients were taking benzbromarone at any time.

Benzbromarone is a long-term treatment for gout, but, within a given time period, many patients stop while others start. Benzbromarone is, like allopurinol, used for the prevention of gout and a similar turnover of treatment can be assumed. In an American survey on the use of allopurinol, 61% of patients started treatment in the year before the index date.[105] Assuming a constant number of patients taking benzbromarone at any time (18 000; i.e. the number of patients ceasing treatment equals the number starting treatment in any year) and a similar turnover to that of allopurinol (i.e. 61% per year), the total number of patients taking benzbromarone over a 6-year period should be approximately 84 000 ($18\,000 \times (100 + 6 \times 61)/100$). As noted above, a maximum of five patients had hepatotoxicity from benzbromarone and, consequently, the incidence of hepatotoxicity from benzbromarone is estimated at 1 in 17 000 (84 000/5) patients. This incidence is, of course, approximate. The incidence may be 1 in >17 000 because:

- perfect compliance was assumed;
- no hepatotoxicity was reported before 1994 and there has been no published report of hepatotoxicity after 2004, despite its continuing availability in some countries (table I).

On the other hand, the incidence is 1 in <15 100 if:

- the turnover of patients taking benzbromarone is less than 61% annually.
- some cases of hepatotoxicity in Europe were not detected or not reported.

It should be noted that our estimate of the risk of hepatotoxicity in European patients is of the same order as the risk of hepatitis *induced by all drugs in the whole population* of a French province (1 in 14 000).[106] However, only 2 of the 34 cases in France died compared with 9 of 11 patients who were reported to have benzbromarone-induced disease. From the number of Japanese patients with hepatitis attributed to benzbromarone, the risk of hepatotoxicity is likely to be higher in Japan than in Europe, but we were unable to gain any information on the number of prescriptions of benzbromarone in Japan and, therefore, could not estimate the risk of hepatotoxicity from benzbromarone in that country.

6.6 Comparison of Risk of Benzbromarone with Alternative Pharmacotherapies

6.6.1 Allopurinol

Patients taking allopurinol have a high incidence of rash, in the order of 1–2%. Of more concern are the rare life-threatening reactions,[46,107,108] such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which have a mortality rate of 10–30%.[46,109] It is difficult to estimate the incidence of these reactions; however, an approximation can be determined from data in Seattle (WA), US and Australia. In Seattle, the overall incidence of hospitalization for erythema multiforme, SJS and TEN has been estimated at 4.2 per million patient-years.[110] It is estimated that 5% of SJS and TEN cases are attributed to allopurinol[111] and thus, the incidence of these reactions due to allopurinol is about 0.21 per million person years. For every 1 million persons in Australia, 7300 defined daily doses of allopurinol are taken.[112] This figure is calculated using an allopurinol dose of 400 mg/day. Our survey of the average dose of allopurinol (unpublished) in hospitalized patients indicates that the mean daily dosage of allopurinol is 217 mg/day but the mean dose is probably closer to 250 mg in gouty patients, overall. Assuming this mean daily dose of 250 mg, 11 680 patients per million of the total population are administered 250 mg allopurinol daily. Assuming a similar incidence of severe cutaneous reactions as in Seattle, the annual incidence of these severe reactions is approximately 1 in 56 000 (11 680/0.21) patients treated with allopurinol. This is clearly a very approximate value and does not account for potential inter-racial differences in the incidence of SJS and TENS or the risk of these reactions due to allopurinol. However, the incidence is almost certainly higher in Chinese patients because of the much higher prevalence in this group of HLA-B*5801 allele which is associated with severe cutaneous adverse reactions to allopurinol.[113]

As discussed above, the severe toxicity of allopurinol has been associated with the excessive

accumulation of oxypurinol in patients with renal impairment.[57] For optimal hypouricaemic effects, it is recommended that the dosage of allopurinol in patients with normal renal function may have to be increased to 800 mg/day,[51] well above the usual daily doses of 300 mg. This increases the plasma concentrations of the active metabolite, oxypurinol; however, there are no data on any change in the risk of severe toxicity in patients with normal renal function. As noted above, a very strong genetic association has been noted recently in Chinese patients between the development of severe hypersensitivity reactions and the HLA-B*5801 allele.[113] However, in patients with this allele, the association between renal impairment and the development of severe adverse reactions to allopurinol was still maintained, with a higher incidence of renal impairment in patients with toxicity than in tolerant patients.

Overall, the risk of severe adverse reactions from allopurinol appears to be somewhat less than the risk of hepatotoxicity from benzbromarone. However, risk management of allopurinol presents difficulties that may not be apparent from the comparison of the crude risks. Patients with substantial renal impairment should be administered low doses of allopurinol in order to prevent excessive accumulation of oxypurinol. Benzbromarone may be a useful hypouricaemic drug in such patients, provided that their CL_{CR} is not below approximately 20 mL/min, conditions in which benzbromarone is an inadequate hypouricaemic agent. Febuxostat may be a useful hypouricaemic drug in such patients if it is approved for general marketing.

6.6.2 Combination of Allopurinol and Benzbromarone

The low-dose combination of allopurinol (100 mg) and benzbromarone (20 mg) obviously delivers lower-than-usual therapeutic doses of both drugs except in patients with substantial renal impairment, for whom the recommended dose of allopurinol is 100 mg/day.[49] We have found literature reports on 312 cases of severe cutaneous toxicity due to allopurinol (unpublished results). None of these patients received allopurinol and benzbromarone in combination, although several patients with renal impairment developed severe cutaneous reactions while taking allopurinol 100 mg/day.[113]

6.6.3 Probenecid

Reported adverse reactions to probenecid have less serious implications than benzbromarone. There have only been two reports of life-threatening events associated with probenecid; SJS[114] in one patient and membranous glomerulonephritis in another.[115] Concerns raised regarding the use of probenecid are its propensity to cause nephrolithiasis during initiation of therapy and lack of efficacy in patients with moderate to severe renal impairment. Probenecid also must be administered twice daily as opposed to the more convenient once-daily dosage regimen of benzbromarone. The problem of reduced efficacy in patients with renal impairment also applies to sulfinpyrazone and, to a lesser extent, benzbromarone. Probenecid also decreases the clearance of a number of drugs such as penicillins, cephalosporins, salicylates, paracetamol (acetaminophen) and indomethacin.[116] The decreased renal clearances and the consequent higher plasma concentrations of penicillins and cephalosporins are clinically useful in patients with some severe infections.

6.6.4 Sulfinpyrazone

Like other uricosuric drugs, sulfinpyrazone can cause nephrolithiasis, and alkalinization of urine or maintenance of a high urine flow rate is recommended. A metabolite of sulfinpyrazone inhibits cyclooxygenase and it is therefore not surprising that sulfinpyrazone causes adverse effects that are typical of NSAIDs. These include the precipitation of asthma in some aspirin-sensitive asthmatic patients,[117] the renal retention of sodium, substantial renal impairment in some patients and gastrointestinal irritation.[118] It is contraindicated in patients with active peptic ulcer.[118] It can also cause blood dyscrasias,[118] as is well known from its close analogue, phenylbutazone.

Sulfinpyrazone interacts with several other drugs. It increases the plasma concentrations of phenytoin and warfarin.[119] Conversely, sulfinpyrazone decreases the plasma concentrations of ciclosporin[120] and, as is the case with

probenecid, sulfinpyrazone inhibits the renal clearance of penicillins.[119] Sulfinpyrazone also decreases the hypotensive activity of oxprenolol and, possibly other antihypertensives, because of its inhibition of prostaglandin synthesis.[121]

Overall, the adverse reactions and drug interactions of sulfinpyrazone make its clinical use difficult and rarely justified.

6.6.5 Febuxostat

There have been some reports of abnormal liver function tests with febuxostat in clinical trials.[89] No cases of serious hepatotoxicity have been reported but the total exposure to the drug is low as this drug is not yet approved for marketing.

7. Recommended Use of Benzbromarone: Prevention of Hepatotoxicity

It is difficult to determine the risk factors for hepatotoxicity with benzbromarone, as only a few cases are available for examination. The active metabolite of benzbromarone, 6-hydroxybenzbromarone has been patented recently (European patent no. 1767531) with the claim that it is "non-hepatotoxic".[5] However, the publication of human trials is required to substantiate this interesting claim. Utilization of the metabolite would also overcome the potential poor response likely to be encountered in individuals deficient in CYP2C9.

Benzbromarone is currently marketed by different companies in several countries including Japan and Germany without restrictions beyond those expected of any prescription medicine. The current prescriber's information for benzbromarone from Torii Pharmaceutical Co. (available from the authors) recommends monitoring liver function within 6 months of commencement of therapy and lists liver impairment as a contraindication. This advice is consistent with the recent recommendations of European Union League Against Rheumatism.[122]

Here we propose a more cautious, yet practical, model for the responsible clinical use of benzbromarone:

- Probenecid should be considered as an alternative when therapy with allopurinol would normally be indicated but happens to be unsuccessful or insufficient. Sulfinpyrazone is a possible alternative uricosuric agent but is unavailable in many countries and, in countries where available, its problems and contraindications should be considered.
- If probenecid is contraindicated, ineffective or unavailable, then benzbromarone alone or the low-dose combination of allopurinol and benzbromarone should be considered.
- Asymptomatic hyperuricaemia is presently not an indication for urate-lowering pharmacotherapy and should be a definite contraindication for benzbromarone use. It is of note that the use of benzbromarone only for recurrent gout, not asymptomatic hyperuricaemia, would have prevented three of the four published cases of hepatotoxicity. However, if plasma urate concentrations are well above the upper limit of normal and this elevation occurred suddenly or is very likely to occur over a short period of time following, for example, cytotoxic therapy, then hypouricaemic therapy, such as benzbromarone, may be appropriate.
- Liver function tests should be performed regularly and more intensively in the first months of therapy. This is a very contentious and difficult area, particularly because the four published cases do not indicate the rate at which the hepatitis developed. We recommend that liver function tests should be conducted before beginning treatment (baseline), weekly during month 1, fortnightly during month 2, monthly during months 3–6, then every 2 months for the rest of the first year of therapy. Our recommendation concerning the frequent examination of liver function goes beyond the recommendation in the product information in countries where the drug has remained available. However, the drug was removed by Sanofi-Synthélabo because of hepatotoxicity. In order to gain support for the use of benzbromarone in countries where access is restricted, we believe that rigorous testing of liver function, which may detect early signs of hepatotoxicity, is prudent.

- Patients should be advised to watch for adverse symptoms such as nausea, vomiting, yellow eyes, abdominal pain or dark urine and to stop the drug and report to their doctor immediately if such signs occur.
- Benzbromarone should be started at a low dosage (e.g. 25 mg/day), and the dosage gradually increased, as required, over the first 6 months based on plasma urate concentrations. The maximum dosage should not exceed 200 mg/day. There is no evidence about whether or not dosages above the standard (100 mg/day) increase the risk of hepatotoxicity.
- The concomitant use of complementary medicines such as herbal medicines that may have potential to cause hepatotoxicity or interfere with drug metabolism should be avoided.
- Benzbromarone should not be used in patients with hepatic diseases. Although benzbromarone has been administered successfully to a small number of patients with cirrhosis, this is not recommended. Benzbromarone should be used with caution with other potentially hepatotoxic drugs, including intake of alcohol beyond recommended daily limits. It should be noted however, that alcohol tends to increase the plasma concentrations of urate and, consequently, its intake for any gouty patient is recommended to be no more than 21 units per week for men and 14 units per week for women plus 3 alcohol-free days each week.[51]
- In cases of apparent hepatotoxicity due to benzbromarone, genotyping with respect to CYP2C9 should be carried out.
- A high urinary output or alkalinization of urine is required to prevent precipitation of uric acid within the kidney tubules and subsequent nephrolithiasis.

8. Conclusions

We have presented evidence of both benefits and risks associated with the use of benzbromarone. It is a potent, long-acting uricosuric agent that is effective in controlling hyperuricaemia. Compared with the alternatives, benzbromarone is at least equally efficacious and may be a safe and effective alternative in the majority of patients, including those with moderate renal impairment, although further studies are needed in this patient group. The major hypouricaemic drug is allopurinol but this, as discussed in this review, is associated with extremely severe toxicity in a small number of patients.

The major risk with benzbromarone use is hepatotoxicity, although, as we have discussed, the incidence appears to be very low and comparable to the general prevalence of drug-induced hepatotoxicity. Most reports of severe hepatotoxicity have been in patients from Japan. The factors contributing to this possible causal association of benzbromarone with hepatotoxicity are unknown but could include differences in metabolism resulting from, for example, CYP2C9 polymorphisms. Possibly concomitant use of complementary medicines needs to be considered. Other adverse reactions associated with benzbromarone are diarrhoea and urate calculi, but these are not more frequent than for other uricosuric agents.

Benzbromarone was withdrawn from the market by the manufacturer after warnings to doctors by Sanofi-Synthélabo failed to prevent further cases of hepatotoxicity.[101] In the absence of all the available data, we are unable to provide a precise quantitative assessment of the risk of hepatotoxicity. However, the risk may be comparable to that of drugs known to cause serious hepatotoxicity but that are still available for prescription, e.g. flucloxacillin and isoniazid.[103]

Benzbromarone is likely to be beneficial to patients with gout, especially when allopurinol and/or probenecid are insufficiently effective or not indicated. The risk of benzbromarone-induced hepatotoxicity is very low, and may be managed by very careful patient selection and monitoring of liver function. We conclude that the withdrawal of benzbromarone from the market in major developed countries and failure to register the drug as a result in others was not in the best interests of many patients with gout. We contend that judicious selection and use of the drug combined with careful titration of the dose, and monitoring by both the

physician and patient should allow access to the drug. In countries where it is unavailable, we recommend that specialist rheumatology and nephrology associations along with patient organizations marshal the arguments for the availability of benzbromarone as a prescription option for patients with gout where other established pharmacotherapies are insufficient or contraindicated.

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