Author's reply

Sir—O M Kon and D S Robinson reference a meta-analysis on methotrexate treatment.[1] This study showed that methotrexate treatment resulted in modest steroid-sparing effects, similar to that observed with cyclosporin. However, Marin concluded that long-term studies of both steroid and methotrexate toxicities were necessary before methotrexate could be recommended for routine clinical use. I do not disagree with Kon and Robinson that these alternative anti-inflammatory agents could be considered in certain patients with severe steroid toxicity. In these instances, the risk-benefit ratio would need to be assessed for each individual: this is different from a general recommendation for their use in all patients with severe asthma

A B Kay and N C Barnes draw attention to their study showing the steroid-sparing effects of cyclosporin in steroid-dependent asthmatics.[2] The study referred to in the table was their earlier investigation showing improvement in lung function with cyclosporin.[3] The aim of this table was to comment on steroid-sparing effects only, and this fact was signalled in the original title for the figure. Unfortunately, "steroid-sparing" was omitted from the title in the published versions.

S H Lock and co-workers' study[2] shows variable steroid-sparing effects in people with chronic asthma. The difference between the mean daily use of prednisolone in the cyclosporin and placebo treated groups was modest (4·4 mg). Although greater reductions in steroid use were achieved during the later weeks of the study, it was not clear that these reductions could be maintained with continued use. Whether the reduction in steroid toxicity could justify the additional toxicity incurred with cyclosporin is conjectural. Although the renal impairment incurred with cyclosporin was said to be reversible, longer treatment with low-dose cyclosporin has resulted in permanent morphological renal damage.[4] Aside from issues of drug toxicity, the use of cyclosporin does not lend itself to routine management. Careful monitoring is essential and rigorous attempts at steroid reduction are necessary to achieve the steroid-sparing effects cited.

R Madhok and colleagues' remarks about terminology in describing these agents is appreciated. I did originally refer to these agents as alternative anti-inflammatory drugs, but this was changed for the published version. Although the designation alternative anti-inflammatory agents is commonly used in pulmonary research and published work, its meaning is not obvious to a general audience. The terms disease-modifying and steroid-sparing agents seem more appropriate.

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1 Marin MG. Low-dose methotrexate spares steroid useage in steroid-dependent asthmatic patients: a meta-analysis. *Chest* 1997; **112:** 29–33.

2 Lock SH, Kay AH, Barnes NC. Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma. *Am J Respir Crit Care Med* 1996; **153:** 509–14.

3 Alexander AGN, Barnes NC, Kay AB. Trial of cyclosporin A in corticosteroid-dependent chronic severe asthma. *Lancet* 1992; **339:** 324–28.

4 Zachariae H, Kragballe K, Hansen HE, et al. Renal biopsy findings in long term cyclosporin treatment of psoriasis. *Br J Dermatol* 1997; **136:** 531–35.

Malarone-donation programme in Africa

Sir—We welcome the addition of atovaquone to the short list of antimalarial drugs that are effective against multidrug-resistant falciparum malaria. However, the possible negative effects of Glaxo's planned donation programme of Malarone (atovaquone-proguanil combination) are a cause for concern. We agree with Peter Bloland and colleagues (Nov 29, p 1624)[1] that the disadvantages associated with the introduction of this drug in Africa may outweigh potential benefits.

Do African countries really need one million "free" doses of Malarone each year? Despite the spread of drug resistance, chloroquine is still a useful drug in everyday life. Currently available second-line and third-line drugs are also cost-effective for the management of uncomplicated (amodiaquine, sulfadoxine-pyrimethamine) and severe and complicated (quinine) malaria. Other new antimalarial drugs (mefloquine, halofantrine, artemether, artesunate) are not only expensive but do not have any clear indication for the treatment of indigenous patients, since multidrug resistance has not been fully documented in Africa. Why then add another new drug when there is no well-defined role for Malarone in Africa today?

Rare but severe and potentially fatal adverse effects of mefloquine and halofantrine have been documented in Europe, North America, and Thailand, countries where the health-care system allows pharmacovigilance. If Malarone is distributed in Africa, a country where health-care facilities, follow-up of patients, and compliance are generally poor, who would guarantee the continued safety of the drug?

Furthermore, crossresistance between sulfadoxine-pyrimethamine and Malarone is possible. Our studies show that in-vitro responses of *Plasmodium falciparum* isolates to two dihydrofolate-reductase inhibitors—pyrimethamine and cycloguanil (a biologically active metabolite of proguanil)—are highly correlated, which suggests a real potential for in-vivo crossresistance if the proportion and degree of resistance to one of these two drugs increase in Africa.[2] In addition, the same single-point mutation within the dihydrofolate reductase gene has been associated with resistance to pyrimethamine and cycloguanil.[3,4] The epidemiology of drug resistance in southeast Asia strongly suggests that the widespread use of pyrimethamine led to the development of resistance to pyrimethamine and cycloguanil.[5] Thus, if Malarone is widely used in Africa, its proguanil component will exert drug pressure and may select pyrimethamine-resistant mutants, leading to the spread of resistance to sulfadoxine-pyrimethamine. Such a scenario will be disastrous since sulfadoxine-pyrimethamine has so far been, and still is, a reliable, cheap, and safe alternative to chloroquine throughout Africa.

Another potential difficulty is the selection of correctly diagnosed, eligible patients. It is not clear who would benefit from free medication. Furthermore, as occurred in the Mectizan-donation programme, a limited supply of "free" drugs in areas where demand is high may encourage unauthorised sale, which obviously defeats the humanitarian goal of the donor company. Malarone is a precious new drug that should be used with rationality, for example, in endemic areas where multidrug resistance is prevalent.

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1 Bloland PB, Kazembe PN, Watkins WM, Doumbo OK, Nwanyanwu OC, Ruebush II TK. Malarone-donation programme in Africa. *Lancet* 1997; **350:** 1624–25.

2 Ringwald P, Bickii J, Basco LK. In vitro activity of antimalarials against clinical isolates of *Plasmodium falciparum* in Yaoundé, Cameroon. *Am J Trop Med Hyg* 1996; **55:** 254–58.

3 Basco LK, Eldin de Pécoulas P, Wilson CM, Le Bras J, Mazabraud A. Point mutations in the dihydrofolate reductase-thymidylate synthase gene and

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