Topical azithromycin: new evidence?

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Should mass distribution of azithromycin be in topical rather than oral formulation?

In this issue, Cochereau *et al*[1] present the results of a randomised controlled trial comparing the effectiveness of topical and oral azithromycin for treatment of active trachoma in children ***(see page 667)***.

Trachoma remains a leading cause of blindness in the world, responsible for an estimated 1.3 million cases.[2] The World Health Organization (WHO) recommends the SAFE (Surgery, Antibiotics, Facial cleanliness, Environmental improvement) strategy to control blinding trachoma, which includes the distribution of antibiotics to treat the *Chlamydia trachomatis* infection that causes active trachoma. Until recently, the treatment of choice was topical administration of 1% tetracycline ointment twice daily for 6 weeks or on 5 consecutive days each month for 6 months. This regimen had low adherence because of the long duration of treatment and the discomfort caused by the ointment. An alternative treatment is a single oral dose of azithromycin. Observational studies suggest that oral azithromycin is highly effective at reducing active trachoma and infection with *C trachomatis* in the community,[3–6] although evidence from randomised controlled trials is inconclusive.[7]

Azithromycin is costly, but, thanks to Pfizer's generous donation of the drug, mass distribution has been undertaken in 11 countries in Africa and Asia. Because oral azithromycin can be used to treat other diseases, there is a concern that the donated drug may be used for other purposes. Topical azithromycin is an alternative means of administering treatment for *C trachomatis* because it cannot be diverted for other uses, yet requires a shorter duration of treatment than tetracycline. But evidence is clearly needed to evaluate the effectiveness of topical administration of azithromycin compared with oral delivery (and placebo) in poorer countries.

In the trial published in this issue, children in Pakistan and Guinea Conakry were randomised to topical azithromycin 1.5% (either twice daily for 2 days, or for 3 days) or a single oral azithromycin dose (20 mg/kg) which is now the recommended standard treatment in many trachoma control programmes. The trial showed a high proportion of children cured in all three arms (93.0%, 96.3%, 96.6%, respectively), with no significant difference in efficacy. Does this mean we should switch to mass distribution of topical azithromycin?

Before this question can be resolved, two issues need further consideration: the first is the trial design—the internal validity of the study; the second is whether distribution of topical antibiotics would be a practical solution in reality—the external validity. There is also the question of cost.

TRIAL DESIGN

The trial compared oral and topical azithromycin, but was not placebo-controlled. This is a common problem with trials of antibiotics for trachoma control.[7] In a recent issue of the *British Journal of Opthalmology*, Shapiro *et al*[8] argued convincingly that placebo-controlled trials will provide important information that will advance our understanding of the effectiveness of azithromycin. Some argue that the benefits of azithromycin treatment have been demonstrated so convincingly that use of a placebo arm in a trial would be unethical.[9] This argument is questionable; it is very unlikely that delaying treatment of active trachoma or *C trachomatis* by 6 months to a year will increase the risk of blindness from trachoma in the decades to come, and we still do not know enough about the possible harmful effects of treatment. We also know that prevalence of trachoma can dramatically decline even without any specific intervention.[10]

EXTERNAL VALIDITY

The second concern is that the trial was conducted in Guinea Conakry and Pakistan. The prevalence of trachoma in the districts in Pakistan was not sufficiently high to warrant mass distribution of antibiotics according to the WHO criteria, and the area in Guinea Conakry only just passed the threshold for treatment. This makes it unclear how far these results are generalisable to trachoma endemic communities where patterns of transmission and re-emergence may differ.

COST EFFECTIVENESS

It is regrettable that there was no reported comparison of cost (although perhaps this may follow). It is likely that topical azithromycin distribution was more expensive as it required multiple visits by health workers, whereas oral azithromycin was distributed in a single dose. Cost effectiveness is a vitally important issue in trachoma control programmes. Leakage of the donated drug to other forms of intervention would also have to be considered in any real-world economic model.

OPERATIONAL ISSUES OF TOPICAL AZITHROMYCIN

Putting aside methodological issues, let us focus on delivery. As topical azithromycin is administered over 3 days, compliance or adherence may be less, and costs and organisational complexities may be increased for the distribution programme.

If we assume that topical treatment is as cost effective as oral azithromycin, should WHO recommend its mass distribution in its topical rather than oral formulation? One possible advantage of oral azithromycin is that it clears nonocular reservoirs of *C trachomatis* (such as the nasopharynx), and a switch to topical azithromycin may mean that these nonocular reservoirs are not eliminated. Therefore the re-emergence of trachoma could be more frequent after topical administration. Although not seen in the trial, the situation may be different in hyperendemic areas, or where there is no simultaneous distribution of soap, health promotion and delivery of oral azithromycin to all members of affected families.

Although the trial results indicate that topical azithromycin is as efficacious as oral azithromycin, further randomised placebo-controlled trials assessing the effectiveness of mass distribution of azithromycin are needed. Clusters randomly allocated to treatment (perhaps testing several doses or distribution frequencies) or placebo should provide the basis for measuring both cost and effectiveness of the interventions. The sample size needed for such studies will depend on the expected effect size. If the expected effect of azithromycin is so great, then large-scale trials will not be needed, although this has so far not been demonstrated in existing studies. These trials will be costly but should allow the most cost-effective protocols for the distribution of the drug to be identified, and so are ultimately likely to be money saving.

Surely, the best possible evidence for effectiveness and safety of azithromycin is needed before any population, particularly the poor and underprivileged,

is subjected to its mass distribution in whatever formulation.

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Asymptomatic choroidal metastases

Decreased prevalence of asymptomatic choroidal metastases in disseminated breast and lung cancer: argument against screening

Sinead Fenton

Asymptomatic choroidal metastases in disseminated breast and lung cancer

Intraocular metastases are the most common malignancy of the eye, and the primary cause is breast cancer followed by lung cancer.[1] The high incidence of breast cancer (one in every eight women are affected) and prolonged survival because of effective treatment explains in part its metastatic frequency.

Ocular metastases most frequently occur to the highly vascular choroid. The incidence of asymptomatic choroidal metastases among patients with breast carcinoma in clinical series has been reported to vary between 8 and 10%.[2 3]

The incidence of ocular metastases in autopsy studies is expectedly higher, since occult microscopic disease is detected.

Bloch and Gartner [4] observed ocular metastases in 36% of patients who died of breast cancer. Font and Ferry[5] found a similar incidence of ocular metastases, in 41% of patients who died of breast cancer.

The figures from some of these series are old and outdated.

In the January issue of this journal Barak *et al*[6] report on the current incidence of asymptomatic choroidal metastases in patients with disseminated breast or lung cancer. In their clinical series of 169 patients, they report a 0% incidence of choroidal metastases in patients with disseminated breast cancer, and a 2% incidence in patients with lung cancer.

We carried out a similar screening programme in 68 asymptomatic patients with metastatic breast carcinoma.[7] We also found a similar incidence of 0% for choroidal metastases.

On the basis of these reported figures, a screening programme for asymptomatic choroidal metastases cannot be justified. Why are these figures so low?

Enhanced systemic oncological treatments with chemotherapy and hormonal therapy for metastatic disease may cause regression of choroidal metastases. Barak *et al* noted that chemotherapy agents such as taxanes are known to penetrate choroidal tissues, and that choroidal metastases are sensitive to these agents, resulting in their reduced detection rate.

The cost of performing numerous examinations on unaffected individuals is obviously high, and the yield is low.

At present, there is not enough evidence to suggest that ophthalmologists should have an active role in screening asymptomatic patients.

In my opinion, resources should be directed towards promptly investigating and managing patients with a history of disseminated breast cancer who report any visual loss or metamorphopsia. Visual loss in these patients represents severe dysfunction, and early treatment with radiation therapy is of paramount importance to maximise their quality of life.

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