Buruli ulcer: cured by 8 weeks of oral antibiotics?

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In 1998, at a special WHO conference on Buruli ulcer held in Yamoussoukro, Côte d'Ivoire, delegates and heads of state of affected countries recognised Buruli ulcer as a damaging disease about which little was known. Importantly, there seemed to be no reliable chemotherapy, leaving wide excisional surgery and grafting as the only effective treatment.[1] Buruli ulcer is caused by *Mycobacterium ulcerans*—an environmental pathogen with a unique virulence determinant—a potent locally acting toxin. Clinically, Buruli ulcer is a destructive infection of the skin and soft tissue, which can result in severe tissue destruction followed by scarring and contracture. It affects healthy people of all ages, but in Africa mostly children and adolescents because of the young population. Although recorded in 33 countries, Buruli ulcer is of particular concern in certain regions of Africa and Australia.[2]

In *The Lancet*, Richard Phillips and colleagues[3] report an open-label, non-inferiority, phase 3 randomised trial, which is the culmination of a journey WHO began in 1998. The trial compared the efficacy and tolerability of fully oral rifampicin 10 mg/kg plus clarithromycin 15 mg/kg extended release once daily for 8 weeks (RC8) with the WHO provisionally recommended standard of oral rifampicin 10 mg/kg plus intramuscular streptomycin 15 mg/kg once daily for 8 weeks (RS8). 297 people with PCR-confirmed Buruli lesions (≤10 cm in diameter) in Ghana and Benin were randomly assigned; median age was 14 years (IQR 10–29) and 153 (52%) participants were female. The primary endpoint was lesion healing without recurrence at 52 weeks. In the RS8 group, the primary endpoint was met in 144 (95%, 95% CI 91–98) of 151 participants compared with 140 (96%, 91–99) of 146 in the RC8 group, establishing non-inferiority of the newer fully oral regimen. Surgery was not required for cure and only four patients (two in each study group) required skin grafts to repair defects. Both regimens were generally well tolerated, but RS8 was associated with eight cases of otovestibular toxicity compared with only one case in the RC8 group. No residual functional limitation was seen in either group at 52 weeks.

The headline finding of the trial is clear and promising: Buruli ulcer was curable with an 8-week course of oral antibiotics and surgery was not required in these patients. So how did this radical change in treatment approach come about? *M ulcerans* is related to *Mycobacterium marinum*, *Mycobacterium tuberculosis*, and *Mycobacterium leprae*, which are all susceptible to antimycobacterial antibiotics, so it was curious that *M ulcerans* appeared not to be, at least in early field studies.[4] Part of the reason for this perception might have been paradoxical worsening of the appearance of lesions during treatment.[5,6] However, a key pilot study sponsored by WHO in a small group of people in Ghana with early Buruli lesions[7] showed that rifampicin and streptomycin could microbiologically sterilise early Buruli lesions, leading to provisional WHO advice for the medical management of Buruli ulcer.[8] Experience built confidence in this regimen[9] and some centres in Africa also reported promising results when oral rifampicin was combined with oral clarithromycin, sometimes without any surgery being required.[10] In Australia, intramuscular streptomycin was not used, but it became apparent that rifampicin-based fully oral regimens reduced relapse after surgery[11,12] and could often replace surgery as definitive treatment.[13,14]

Now, Phillips and colleagues have shown that rifampicin combined with clarithromycin is non-inferior to RS8, and is safer. This much anticipated trial provides us with a high degree of confidence that an 8-week course of oral rifampicin and clarithromycin should now be the cornerstone of the treatment of Buruli ulcer everywhere. However, this finding does not mean that Buruli ulcer is cured at 8 weeks. Healing of Buruli lesions is

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a slow process. In the study by Phillips and colleagues, the median time to healing was 24 weeks (IQR 8–28) for RS8 and 16 weeks (IQR 8–25) for RC8. Practically, this result means that Buruli lesions are typically not healed at the completion of 8 weeks of antibiotics and it is important for clinicians to understand this. Frequent dressings, support, and reassurance, and, in selected cases, limited surgical debridement or grafting might still be needed.[15] However, we now know that we can trust oral antibiotics for Buruli ulcer, even if this might not be clinically apparent at 8 weeks.

One of the limitations of the study is that the study did not enrol the originally planned number of participants because of slow recruitment, reflecting a general reduction in the incidence of Buruli ulcer in west Africa for reasons that are not clear. Questions remain as to whether we need 8 weeks of treatment or if 4–6 weeks might be sufficient in some cases, whether steroids could reduce inflammatory reactions and improve outcomes, and whether 2 weeks of some of the new antimycobacterial agents in development could suffice.[16] The change in incidence in time and place of Buruli ulcer makes it hard to study and it is a tribute to all involved in this trial that they saw it through, providing clinicians with the key evidence needed to assist people with Buruli ulcer to resume their lives and to put the disease behind them.

I declare no competing interests.

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Treatment of upper urinary tract urothelial carcinoma

Upper tract urothelial (transitional cell) carcinoma (UTUC) is a rare malignant disease occurring in roughly two people per 100 000 population. UTUCs comprise 5–10% of urothelial carcinomas overall.[1] A paucity of dedicated high-level evidence has led to extrapolation from studies of urothelial bladder cancer to establish treatment recommendations. Although UTUC biology and clinical features overlap with those of urothelial bladder cancer, differences exist in gene alteration patterns (eg, *FGFR3* and *HRAS* are more frequently altered in UTUC whereas *TP53*, *RB1*, and *ERBB2* are less frequently mutated), clinical stage at presentation (higher stage at presentation, on average, for patients with UTUC), gender differences (a higher percentage of women get UTUC, although in terms of total numbers they are still in a minority compared with men), and stage-for-stage outcomes (prognosis is poorer for patients with UTUC).[2,3] As with many rare disease settings, patients with UTUC are disenfranchised because dedicated research is challenging.