Management of toxoplasmic encephalitis in HIV-infected adults – a review

Martin Dedicoat, Nigel Livesley

To the Editor: Many patients in Africa present with HIV for the first time when they develop an opportunistic infection such as toxoplasmic encephalitis (TE). Optimal management of opportunistic infections such as TE is important in improving health and allowing patients to benefit from the expanding roll-out of highly active antiretroviral therapy (HAART).[1-3] Possible treatment regimens for TE include pyrimethamine plus sulfadiazine (P+S), pyrimethamine plus clindamycin (P+C), co-trimoxazole, and atovaquone.

The aim of this review was to determine which therapy was most effective for treating HIV-infected patients presenting with a first episode of TE. Primary and secondary prophylaxis of TE were not considered. A full version of this review is available in the Cochrane library.[4]

Methods

Treatment regimens were compared with regard to clinical and radiological response, mortality, morbidity and serious adverse events.

Criteria for considering studies for this review were that studies be randomised controlled trials, and that participants be HIV-infected adults over 18 years of age with radiologically or histologically diagnosed TE. Both patients receiving and not receiving HAART were included. Types of interventions considered were those in which antibiotics were given alone or in combination for the treatment of TE.

Primary outcomes were: (*i*) mortality defined as death during the follow-up period of the study (where possible, death due to TE was examined separately from death due to other causes); (*ii*) clinical response to treatment; (*iii*) neurological outcome; and (*iv*) serious adverse events (as defined by trial researchers).

Secondary outcomes were: (*i*) radiological response to treatment; and (*ii*) minor adverse events (as defined by trial researchers).

Department of Medicine, Ngwelezane Hospital, Empangeni, KwaZulu-Natal
Martin Dedicoat, MB BS, BSc, MRCP, DTM&H, PhD

Department of Medicine, Hlabisa Hospital, KwaZulu-Natal, and Africa Centre for Health and Population Studies, Somkhele, KwaZulu-Natal
Nigel Livesley, MD

Corresponding author: *Martin Dedicoat (mdedicoat@doctors.org.uk)*

The HIV/AIDS Collaborative Review Group Search Strategy provides further details on the search strategy used to identify studies.

Results

Searches revealed almost 1 000 studies related to TE treatment. The majority investigated prophylaxis or were not randomised. Only 3 studies were felt to be of sufficient quality to merit inclusion. A list of excluded studies and the reason for exclusion can be found in the full review.[4]

Dannemann *et al*.[5] and Katlama *et al*.[6] compared P+S with P+C. Torre *et al*.[7] compared P+S with trimethoprim-sulfamethoxazole (TMP-SMX). All 3 protocols allowed crossover to the other treatment arm at the discretion of the investigators if patients were not responding or were suffering from severe adverse events. For the purposes of this review clinical outcomes were analysed as complete or partial resolution versus failure. Patients who crossed over or who were lost to follow-up were analysed as failures.

Dannemann *et al*.[5] assessed 59 patients. Five of 26 patients (19%) randomised to P+C died in the first 6 weeks compared with 2 of the 33 patients (6%) randomised to P+S (relative risk (RR) 3.17; 95% confidence interval (CI) 0.67 - 15.06). Complete or partial resolution (defined as resolution of TE or a greater than 50% improvement in the graded neurological examination) was obtained in 12 patients (46.2%) receiving P+C v. 16 patients (48.5%) receiving P+S (RR 0.95, 95% CI 0.55 - 1.64). Radiological outcomes were analysed as intention to treat regardless of whether patients crossed over or not. Nineteen patients (73%) randomised to P+C and 20 patients (61%) randomised to P+S had complete or partial radiological responses at 6 weeks (RR 1.21, 95% CI 0.84 - 1.73). Sixteen patients (62%) randomised to P+C and 19 patients (58%) randomised to P+S experienced adverse events (RR 1.07, 95% CI 0.7 - 1.63). The types of adverse events were similar in both groups, with rash being the most common adverse event.

Katlama *et al*.[6] assessed 299 patients. Twenty-nine (19%) of the 152 patients randomised to P+C died compared with 22 (15%) of the 147 patients randomised to P+S (RR 1.27, 95% CI 0.77 - 2.11). We were unable to obtain data on the outcomes of patients who crossed over and therefore excluded these data from the analysis. One hundred and ten patients (72%) randomised to P+C and 117 patients (80%) randomised to P+S had complete or partial radiological responses at 6 weeks (RR 0.91, 95% CI 0.8 - 1.03). Ninety-two patients (60%) randomised to P+C and 96 patients (65%) randomised to P+S experienced

at least one adverse event (RR 0.93, 95% CI 0.78 - 1.1). Adverse events were similar in both groups although skin rash, liver toxicity and crystalluria were more common with P+S, while diarrhoea was more common with P+C.

Dannemann *et al*.[5] and Katlama *et al*.[6] were not heterogeneous for the outcomes of mortality, adverse events and radiological outcome. They were, therefore, analysed together for these outcomes. The two treatment arms did not differ for death (RR 1.41, 95% CI 0.88 - 2.28), complete or partial radiological response (RR 0.95, 95% CI 0.84 - 1.07), or adverse events (RR 0.95, 95% CI 0.81-1.11).

Torre *et al*.[7] assessed 77 patients. There were no deaths during the study period. Twenty-eight of 40 patients (70%) randomised to TMP-SMX had a good clinical response compared with 26 (70%) of 37 patients randomised to P+S (RR 1.0, 95% CI 0.74 - 1.33). Twenty-seven patients (68%) randomised to TMP-SMX and 23 (62%) randomised to P+S had a good radiological outcome (RR 1.09, 95% CI 0.78 - 1.51). Five patients (12%) randomised to TMP-SMX and 8 patients (22%) randomised to P+S experienced an adverse event (RR 0.58, 95% CI 0.21 - 1.61). Skin rash was significantly more common with P+S.

We also compared patients who received TMP-SMX or P+C with patients who received P+S. There was no statistically significant difference for death (RR 1.51, 95% CI 0.86 - 2.67).

Discussion

Because of the small number of studies in the final analysis it was not possible to conduct subanalysis of studies. Two studies (Dannemann *et al*.[5] and Katlama *et al*.[6]) compared P+C with P+S. These were analysed together for death, radiological response, and adverse events. The pooled analysis for mortality, radiological outcomes and adverse events revealed no differences between the two treatments. Only Danneman *et al*.[5] was analysed for clinical response, but no difference was found between the two treatments. Therefore P+S and P+C can be considered equivalent for the treatment of acute TE in HIV-infected individuals.

One of the aims of the review was to identify treatments that would be suitable for resource-poor settings where sulfadiazine is often not available despite being on the World Health Organization essential drugs list (complementary list).[8] TMP-SMX was compared with P+S by Torre *et al*.[7] and was not found to be inferior. From this one study the evidence suggests that TMP-SMX, which is cheap and readily available in developing countries, may be suitable first-line therapy for acute TE in HIV-infected individuals. In South Africa TMP-SMX is already recommended in the standard treatment guidelines[9] and essential drugs list as first-line treatment for TE.

The available evidence fails to identify any one superior regimen for the treatment of TE. No significant difference was found between the different treatment regimens. The choice of therapy will often be directed by available therapy. Given the current evidence, TMP-SMX appears to be an effective alternative therapy to P+S for TE in resource-poor settings.

With the advent of combination antiretroviral therapy in high-income countries opportunistic infections such as TE have declined. They remain a large problem in resource-poor settings where frequently patients present to the health services with opportunistic infections and are diagnosed with HIV infection at the same time. Large amounts of donor funding are currently being devoted to improving care of HIV-infected patients in resource-poor settings but the evidence base for how to do this is thin. Further evaluations of treatment available in resource-limited settings will be important to ensure that funds are used efficiently. As a middle-income country with a well-developed health service, South Africa is ideally placed to conduct trials to determine the ideal treatment regimen for TE. Collaboration between centres managing large numbers of patients with TE should be encouraged to achieve this goal.

We wish to acknowledge Krishma Busgeeth from the South African Cochrane Centre, Cape Town, for carrying out the majority of the searches for this review.

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