Second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia: a case series and systematic review

Benfield T, Atzori C, Miller R F, Helweg-Larsen J

CRD summary
The authors concluded that trimethoprim-sulfamethoxazole should be used as second-line treatment for patients with AIDS-associated Pneumocystis jirovecii pneumonia who fail first-line treatment with other regimens. The limited search, incomplete reporting of review methods, differences between studies and lack of direct comparisons between treatments meant that the authors' conclusions may not be reliable.

Authors' objectives
To evaluate second-line salvage treatment of AIDS-associated Pneumocystis jirovecii pneumonia (PCP).

Searching
MEDLINE was searched for studies published up to August 2007. Search terms were reported. No language restrictions were applied. In addition, reference lists were screened.

Study selection
Randomised controlled trials (RCTs), observational studies and individual treatment data from a three-centre study that evaluated second-line salvage PCP treatment in HIV-I-infected patients were eligible for inclusion. Second-line salvage treatment was defined as the treatment given after a change after at least five days of the primary PCP treatment due to suspected treatment failure. Studies in which treatment was changed due to toxicity and studies of eflornithine or trimetrexate were excluded. Patients had to have microbiologically confirmed PCP. The review defined a positive second-line treatment outcome as survival or definitive clinical improvement as defined by the study authors.

For first line-treatment most studies used trimethoprim-sulfamethoxazole (TMP-SMX); other studies used pentamidine, dapsone, clindamycin-primaquine (C-P) or atovaquone. For second-line treatment most studies used pentamidine; other studies used TMP-SMX, C-P, or atovaquone. Where reported, the number of days of failed therapy ranged from four to 21 days.

Two reviewers independently selected studies and resolved disagreements by consensus.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
For each study, numbers of patients with clinical cure or survival were extracted and used to calculate odds ratios (OR) and 95% confidence intervals (CI). One reviewer extracted individual treatment data from the three-centre study. The authors did not state how data were extracted from other studies, or how many reviewers performed the data extraction.

Methods of synthesis
Pooled OR and 95% CI were calculated for each treatment (methods were not reported). Multivariable Cox proportional hazards regression analysis was used to assess the influence of disease severity on mortality three months after the primary diagnosis of PCP using data from the three-centre study; variables included in the model were listed. Heterogeneity was assessed using the $\chi^2$ test. The effect of publication date on treatment efficacy was also examined.

Results of the review
Twenty-nine studies were included (n=1,656 episodes of PCP). These included eight RCTs, four phase 2 trials, two intensive care unit selections, eight observational cohort studies and seven case series. Only 82 (6.9 per cent) of the patients from the three-centre study were included in analyses.
Treatment response rates were 73 per cent for TMP-SMX and 68 per cent for clindamycin-primaquine, resulting in positive outcomes for second-line therapy (OR 2.1, 95% CI: 1.1, 3.2 for TMP-SMX and OR 2.7, 95% CI: 1.3, 4.0 for clindamycin-primaquine). The response rate for pentamidine was 44 per cent, with an increased risk of second line therapy (OR 0.8, 95% CI: 0.6, 1.0). Atovaquone showed no significant benefit as a second line treatment.

Analysis using data from the 82 patients in the three-centre study showed intravenous pentamidine was associated with a significantly increased risk of death at three months compared to TMP-SMZ (adjusted relative risk 12.4, 95% CI: 4.0, 38.3) and that second-line treatment with pentamidine and TMP-SMZ improved over time.

Authors’ conclusions
TMP-SMX should be used as second-line treatment for patients with AIDS-associated *Pneumocystis jirovecii* pneumonia who fail first-line treatment with other regimens. For those failing TMP-SMX treatment, clindamycin-primaquine is an alternative to intravenous pentamidine.

CRD commentary
The review question was clearly stated. Inclusion criteria were defined for intervention, participants, outcomes and study design. Although no language restrictions were applied, limiting the search to studies identified in one database plus references may have resulted in the omission of other relevant studies and raised the potential for publication bias. Methods were used to minimise reviewer error and bias during study selection, but similar methods were either not used for the extraction of data or not described. Study validity was not assessed, so it was not possible to comment on the reliability of the results presented. Data were pooled using meta-analysis, but methods and results of the assessment of heterogeneity were not reported. This meant that it was not clear if results were sufficiently similar across all studies for pooling. In addition, it was not readily apparent how many patients were involved in each analysis and this made it difficult to assess the strength of the findings. The influence of some variables was examined. Conclusions regarding the optimal treatment were based on indirect comparisons between subgroups of trials rather than direct comparisons within trials, therefore, any conclusions drawn about the relative effects of treatments were not definitive.

The limited search, incomplete reporting of review methods, differences between studies and lack of direct comparisons between treatments meant that the authors’ conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that TMP-SMX should be used as second-line treatment for patients who fail first-line treatment with other regimens. For those failing TMP-SMX treatment, clindamycin-primaquine was an alternative to intravenous pentamidine.

Research: The authors did not state any implications for research.

Funding
Not stated.

Bibliographic details

**PubMedID**
18360286

**DOI**
10.1097/QAI.0b013e31816de84d

Indexing Status
Subject indexing assigned by NLM

MeSH
AIDS-Related Opportunistic Infections /drug therapy; Clindamycin /administration & dosage /therapeutic use; Cohort Studies; Humans; Pentamidine /therapeutic use; Pneumocystis jirovecii /isolation & purification; Pneumonia, Pneumocystis /drug therapy /microbiology; Primaquine /administration & dosage /therapeutic use; Salvage Therapy; Treatment Outcome; Trimethoprim, Sulfamethoxazole Drug Combination /therapeutic use

AccessionNumber
12008106988

Date bibliographic record published
03/02/2009

Date abstract record published
10/06/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.