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Voriconazole versus amphotericin B or fluconazole in cancer patients with neutropenia (Review)

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[Intervention Review]

Voriconazole versus amphotericin B or fluconazole in cancer patients with neutropenia

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ABSTRACT

Background

Opportunistic fungal infections are a major cause of morbidity and mortality in neutropenic cancer patients and antifungal therapy is used both empirically and therapeutically in these patients.

Objectives

To compare the benefits and harms of voriconazole with those of amphotericin B and fluconazole when used for prevention or treatment of invasive fungal infections in cancer patients with neutropenia.

Search methods

Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2014, Issue 1 2014), MEDLINE (to January 2014). Letters, abstracts and unpublished trials were accepted. Contact was made with trial authors and industry.

Selection criteria

Randomised clinical trials comparing voriconazole with amphotericin B or fluconazole.

Data collection and analysis

Data on mortality, invasive fungal infection, colonisation, use of additional (escape) antifungal therapy and adverse effects leading to discontinuation of therapy were extracted independently by two review authors.

Main results

Three trials were included. One trial compared voriconazole to liposomal amphotericin B as empirical treatment of fever of unknown origin (suspected fungal infection) in neutropenic cancer patients (849 patients, 58 deaths). The second trial compared voriconazole to amphotericin B deoxycholate in the treatment of confirmed and presumed invasive *Aspergillus* infections (391 patients, 98 deaths). The third trial compared fluconazole to voriconazole for prophylaxis of fungal infections in patients receiving allogeneic stem cell transplantation (600 patients, number of deaths not stated). In the first trial, voriconazole was significantly inferior to liposomal amphotericin B according to the trial authors' prespecified criteria. More patients died in the voriconazole group and a claimed significant reduction in the number of breakthrough fungal infections disappeared when patients arbitrarily excluded from the analysis by the trial authors were included. In the second trial, the deoxycholate preparation of amphotericin B was used without any indication of the use of premedication to counter side effects and replacement of electrolytes or use of salt water. This choice of comparator resulted in a marked difference in the duration of treatment on the trial drugs (77 days with voriconazole versus 10 days with amphotericin B) and precluded

meaningful comparisons of the benefits and harms of the two drugs. The third trial failed to find a difference in fungal free survival or invasive fungal infections at 180 days when voriconazole was compared to fluconazole.

Authors' conclusions

Liposomal amphotericin B is significantly more effective than voriconazole for empirical therapy of fungal infections in neutropenic cancer patients and should be preferred. For treatment of aspergillosis, there are no trials that have compared voriconazole with amphotericin B given under optimal conditions. For prophylactic fungal treatment in patients receiving allogeneic stem cell transplantation, there was no difference between voriconazole and fluconazole regarding fungal free survival or invasive fungal infections.

PLAIN LANGUAGE SUMMARY

Is voriconazole better than amphotericin B or fluconazole to prevent and treat fungal infections in cancer patients with poor immune defence systems

Background

Patients with cancer who are treated with chemotherapy or receive a bone marrow transplant have an increased risk of fungal infections. Such infections can be life-threatening. Antifungal drugs are therefore often given to prevent fungal infections in such patients, either when these patients are known to have a fungal infection or when such an infection is suspected. We reviewed the evidence about the effect of voriconazole compared to amphotericin B or fluconazole to prevent or treat fungal infections in cancer patients with a poor immune system to provide defence.

Study characteristics

We identified three studies. Our most recent search for studies was done in January 2014.

One trial compared voriconazole to liposomal amphotericin B in 849 men and women (58 deaths) with cancer and a poor immune system. Treatment was most often given for seven days. The treatment was provided in patients where a fungal infection was suspected because they had a fever that could not otherwise be explained.

The second trial compared voriconazole to amphotericin B deoxycholate in 391 men and women (98 deaths) with cancer and a poor immune system. Voriconazole was given for 77 days on average whereas liposomal amphotericin B deoxycholate was given for 10 days on average. The treatment was given when patients were known or suspected to have a specific fungal infection (Aspergillus).

The third trial compared voriconazole to fluconazole in 600 men and women (the number of deaths was not stated) with cancer who had undergone a transplantation of their bone marrow after high-dose chemotherapy that suppresses their immune system. The treatment was given to prevent fungal infections.

All studies were sponsored by the manufacturer of the study drug, voriconazole.

Key results

This review found that voriconazole was inferior to liposomal amphotericin B for treatment of suspected fungal infections. More patients treated with voriconazole died and a claimed benefit in terms of fewer new fungal infections disappeared when we included patients that had been excluded without good reason from the analyses presented in the published article. We also found that voriconazole has not been compared with amphotericin B when given under optimal conditions for the treatment of invasive aspergillosis, and that voriconazole was no better than fluconazole in patients undergoing a bone marrow transplantation for preventing invasive fungal infections or for extending the time patients survive without a fungal infection.

Quality of the evidence

The first and second trial were seriously misleading. The first trial analysed the results of the study in a different way from that originally planned, which favoured the study drug voriconazole. The second study compared voriconazole to a drug (liposomal amphotericin B) that was given at substandard dose, which means the results of the study are not meaningful. The third study should have presented how many patients died but did not.

BACKGROUND

Opportunistic fungal infections are a major cause of morbidity and mortality in neutropenic patients (Richardson 1998). The mortality in patients with candidaemia or deep tissue infection is about 50% (Edwards 1997). Since it is difficult to diagnose an invasive fungal infection with certainty (Verfaillie 1991; Walsh 1990), antifungal agents are not only used therapeutically but also prophylactically in patients undergoing antileukaemic chemotherapy or bone marrow transplantation; or empirically if these patients have persistent fever of unknown origin and a fungal infection is suspected.

Voriconazole is a broad-spectrum triazole that is active in vitro against various yeasts and moulds, including *Aspergillus* species (Espinel-Ingroff 2001). It is a derivative of fluconazole but with a broader spectrum and it can be given orally and intravenously (Pearson 2003).

OBJECTIVES

To compare the benefits and harms of voriconazole with those of amphotericin B and fluconazole when used for prevention or treatment of invasive fungal infections in cancer patients with neutropenia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials, irrespective of language of the report, which compared voriconazole with amphotericin B or fluconazole in neutropenic cancer patients were eligible. Trials solely concerned with prevention or treatment of oral candidiasis and trials using inadequate randomisation methods, such as allocation based on date of birth, were not accepted.

Types of participants

Patients with cancer complicated by neutropenia

Types of interventions

Experimental: voriconazole given intravenously or orally
Control: amphotericin B or fluconazole given intravenously or orally

Types of outcome measures

- Total mortality (all deaths regardless of cause, preferably after three months) as this is a measure of long-term survival previously used in similar studies (Johansen 2002)
- Invasive fungal infection (defined as positive blood culture, lung infection confirmed histopathologically, or microscopically confirmed deep tissue involvement)
- Colonisation (as defined by the trial authors)
- Use of additional (escape) antifungal therapy
- Adverse effects leading to discontinuation of the therapy and other important adverse effects

Search methods for identification of studies

Electronic searches

The Cochrane Central Register of Controlled Trials (CENTRAL) was searched to January 2014 with the terms for drugs and diseases and with the addition of bone next marrow.

We searched MEDLINE (PubMed) from 1966 onwards. One or more of the following: clinical-trial [pt] OR clinical-trials [MeSH] OR placebo* OR comparative-study [MeSH] OR random* OR control* OR blind* was combined with one or more of the following: voriconazol* AND (amphotericin OR fluconazol*) and with one or more of the following: bone-marrow OR cancer* OR fungemia OR hematologic* OR malignan* OR neoplas* OR neutropeni* OR granulocytopeni* OR leukemi* OR lymphom*. The latest searches for this review were made in January 2014.

Searching other resources

Letters, abstracts and unpublished trials were accepted in an attempt to minimise the impact of publication bias. We attempted to obtain information about trials not registered in MEDLINE, including unpublished ones, by contacting drug manufacturers, scanning reference lists of articles, and contacting trial authors.

Data collection and analysis

Data extraction and management

Decisions on which trials to include and which variables to use when options were available for the same outcome were taken independently by two review authors, based on the methods sections of the trials. Details on diagnosis, drug, dose and duration of treatments, criteria for starting treatment, rules for additional (escape) antifungal therapy, length of follow-up, randomisation and blinding methods, number of randomised patients, exclusions after randomisation, deaths, invasive fungal infections, colonisation, use of escape drug, total number of dropouts, dropouts because of adverse effects, and other important adverse effects were extracted independently by two review authors. Differences in the data that were extracted were resolved by discussion.

We defined invasive fungal infection as a positive blood culture, lung infection confirmed histopathologically, or microscopically confirmed deep tissue infection. We excluded cases of oropharyngeal, oesophageal and vulvovaginal candidiasis, skin infections, *Candida* in the urine, and vaguely described infections.

We used MEDLINE to obtain the trial authors' most recent addresses. All first authors were asked to answer additional questions. We specifically asked for mortality data three months after study entry for all patients, including those the trial authors might have excluded after the randomisation. We looked for details on the randomisation process, especially whether treatment allocation was concealed, for example central randomisation or use of opaque, sealed, sequentially numbered envelopes.

Data synthesis

Results were not pooled because of heterogeneity in trial design. We considered trials that had adequate concealment of allocation, were double blind, and included all randomised patients in the analyses of total mortality and invasive fungal infection to have a lower risk of bias than other trials.

RESULTS

Description of studies

We identified four trials and excluded one in which all patients had oesophageal candidiasis, which is not an invasive fungal infection according to our inclusion criteria; in addition, 94% of the patients had AIDS (Ally 2001).

The antifungal agent was given empirically in one trial (Walsh 2002), as treatment in one trial (Herbrecht 2002) and for prophylaxis in one trial (Wingard 2010).

Walsh 2002 mainly included patients with leukaemia but also other types of cancer, and patients who had undergone transplantation with haematopoietic stem cells. Voriconazole was administered intravenously with a loading dose of 6 mg/kg twice within the first 24 hours, and a maintenance dose of 3 mg/kg twice daily, or 200 mg orally twice daily, after at least three days of intravenous therapy. The comparator was liposomal amphotericin B, which was administered intravenously at 3 mg/kg/day without change of dosage.

Herbrecht 2002 included patients with definite (39%) or probable (61%) invasive Aspergillus infection, with a similar distribution of underlying disease as in the trial by Walsh et al (Walsh 2002) apart from 11% that had other causes of immunosuppression. Voriconazole was administered intravenously with a loading dose of 6 mg/kg twice within the first 24 hours and a maintenance dose of 4 mg/kg twice daily for at least seven days, followed by 200 mg orally twice daily. The comparator was intravenous amphotericin B deoxycholate, which was administered in a dose of 1 to 1.5 mg/kg/day; there was no mention of use of premedication to prevent infusion related toxicity or replacement of electrolytes and administration of salt water to prevent nephrotoxicity.

Wingard 2010 included patients that received allogeneic haematopoietic stem cell transplantation for leukaemia or other haematopoietic disorders. Prophylaxis with 200 mg voriconazole twice daily was compared to 400 mg fluconazole once daily. Both drugs were administered orally. Intravenous therapy in corresponding doses was given if oral treatment was not possible. Children under the age of 12 years received lower doses of either drug according to weight; for fluconazole, the doses were also adjusted according to renal function. Prophylactic drug treatment was provided from day 0 until 100 days post-transplantation.

Three groups of patients considered at high risk of developing invasive fungal infection continued with the drug through to day 180. One group included any patient that received > 1 mg/kg/day of prednisolone, or equal steroid dose on days 90 to 100. A second group included patients that received a T cell-depleted graft and were given immunosuppressive drugs post-transplantation as graft-versus-host disease prophylaxis. The third group included patients who received a T cell-depleted graft and where CD4 counts were < 200 cells/mL on days 90 to 100.

Risk of bias in included studies

One of the three trials was blinded. One used a 'computer-generated randomization system' (Walsh 2002). According to information provided by the sponsor, it was possible that the investigator could foresee what the next treatment would be for about half the participants since patients were randomised in blocks of two. The second trial used central randomisation with minimisation using four stratification factors (Herbrecht 2002). Both trials defined a 'modified intention-to-treat group' as patients who received at least one dose of the drug; in the trial by Herbrecht et al (Herbrecht 2002) the diagnosis of invasive infection also needed confirmation by a data-review committee. Only data from these patients were analysed. Herbrecht et al described their study as two studies, based on two individual but identical protocols that were developed for two groups of countries, and noted that it was preplanned to combine the results.

The third trial was double blind (Wingard 2010). Both the clinicians and the patients, and the data-review board, were blinded. The drugs were in identical capsules and, to maintain blinding, placebo was given in the fluconazole arm as this drug was administered once daily whereas voriconazole was administered twice daily.

Patients were randomised in a 1:1 ratio by permuted random blocks. It was not clear whether the randomisation process was concealed.

Effects of interventions

Two included trials (Herbrecht 2002; Walsh 2002) were sponsored by Pfizer. The authors of the trials did not provide responses to our requests for additional information, and we therefore contacted Pfizer. The third trial (Wingard 2010) was supported by a grant from the National Institutes of Health and a grant from Pfizer. Several of the authors declared conflicts of interest in relation to Pfizer.

In the trial by Walsh et al (Walsh 2002), the total number of randomised patients was not stated, but according to additional data provided by the sponsor 22 more patients than those accounted for in the trial report had been randomised, 435 to the voriconazole group and 436 to the liposomal amphotericin B group; one of these patients, from the voriconazole group, died. The trial report described 849 patients who received at least one dose of trial drug, but only 837 patients were included in the analysis. The reasons for the additional 12 exclusions and their group assignment were not mentioned.

The trial by Herbrecht et al (Herbrecht 2002) randomised 391 patients but excluded 50 patients in the voriconazole group and 52 patients in the amphotericin B group because the diagnosis of invasive aspergillosis at trial entry could not be confirmed by a blinded data-review committee. An additional 12 patients in the voriconazole group and nine patients in the amphotericin B group were excluded because they did not receive a single dose of the trial drug.

Wingard 2010 included 600 patients from 35 centres with 305 in the voriconazole group and 295 in the fluconazole group. All randomised patients were included in the analyses according to the intention-to-treat principle, but the percentages given for overall survival did not correspond to whole numbers of deaths, which indicates that some patients were missing from the survival analyses. The study drug was discontinued in 41% and 44% of the patients in the voriconazole and fluconazole groups, respectively. Discontinuation was due to protocol-specified reasons in 36% of cases and non-protocol specified reasons in 5% of cases in the voriconazole group, and in 35% and 10% of cases, respectively, in the fluconazole group. The reasons were not further specified.

Total mortality

Walsh 2002: according to table 2 in the article, 33 patients (8%) died in the voriconazole group and 25 (5.9%) in the liposomal amphotericin B group 7 days after the end of therapy. In the footnote to the table, these numbers were 48 versus 31, but according to the sponsor this discrepancy is due to some patients having more than one cause of death. After 30 days 108 patients had died, but this result was not divided into treatment group. According to the sponsor, 62 of these deaths were in the voriconazole group versus 46 in the amphotericin B group. Including all patients and adding the additional death on voriconazole, described above, the relative risk (RR) for mortality was 1.37 (95% confidence interval (CI) 0.96 to 1.96, P value = 0.10, review authors' calculation).

Herbrecht 2002: at the end of the 84-day trial period, the mortality rate was significantly lower in the voriconazole group than in the amphotericin B group, 42 out of 144 (29.2 %) versus 56 out of 133 (42.1 %) (P value = 0.02, log rank test). According to additional data provided by the sponsor, inclusion of the 102 excluded patients gave similar results; there were 177 versus 161 patients in the trial after 14 days and 55 versus 78 deaths after 84 days.

Wingard 2010: after 100 days, 90% (95% CI 86% to 93%) and 85% (95% CI 81% to 89%) of the patients in the voriconazole and fluconazole groups, respectively, were alive (Appendix table S2), but the paper did not give numbers of deaths.

Invasive fungal infection

Walsh 2002: 15 patients (7 persisting from baseline plus 8 new) in the voriconazole group and 23 patients (2 plus 21) in the liposomal amphotericin B group had a documented fungal infection (P value = 0.27, Fisher's exact test, our calculation). The risk difference (RD) was 1.8% (95% CI -1.0% to 4.7%, review authors' calculation).

Herbrecht 2002: a complete response was noted for 30 versus 22 patients (P value = 0.45, Fisher's exact test, our calculation) in the voriconazole and amphotericin B groups, respectively. The RD was 4% (95% CI -5% to 13%, review authors' calculation).

Wingard 2010 :the primary outcome measure was fungal free survival at 180 days. This was 78% (95% CI 73% to 82%) in the voriconazole group and 75% (95% CI 70% to 80%) in the fluconazole group. At 180 days, 55 patients had developed invasive fungal infections in both groups combined. Of the proven invasive fungal infections, five were in the voriconazole group and nine in the fluconazole group. Of the 24 probable invasive fungal infections, 9 were in the voriconazole group and 15 in the fluconazole group; and of the 17 presumed invasive fungal infections, 8 were in the voriconazole group and 9 in the fluconazole group.

The differences were not significant and the cumulative incidence rate of invasive fungal infections was 7% in the voriconazole group and 11% in the fluconazole group (P value= 0.12) at 180 days.

A trend towards fewer *Aspergillus* cases in the voriconazole group at day 180 was described (9 versus 17; P value = 0.09) but the difference was not significant.

Use of additional (escape) antifungal therapy

Walsh 2002: the median duration of therapy was seven days in both groups. No data were given on the use of escape drugs; patients who were unable to tolerate or did not respond to the trial drug were removed from the trial.

Herbrecht 2002: the average duration of therapy was 77 days in the voriconazole group and 10 days in the amphotericin B group. A total of 52 patients in the voriconazole group and 107 patients in the amphotericin B group received an escape drug due to progression of the infection or toxic effects of the therapy. Patients switching to other therapy than the trial drugs remained in the trial.

Wingard 2010: no data on the use of escape therapy after 100 days of follow-up were available, but data after 180 days showed that additional antifungal therapy was given based on the suspicion of a fungal infection in 24% (95% CI 19% to 29%) of the patients in the voriconazole arm and in 30% (95% CI 25% to 36%) of the patients in the fluconazole arm (P value = 0.11 for the difference between groups). The median duration of the empirical therapy was seven days in both groups.

Patients in whom the study drug was discontinued (41% and 44% in the voriconazole and fluconazole groups, respectively) were permitted to receive open label prophylaxis.

Nephrotoxicity

Walsh 2002: 29 patients receiving voriconazole versus 32 patients receiving liposomal amphotericin B experienced a two-fold increase in serum creatinine levels as compared to baseline.
Herbrecht 2002: 2 patients receiving voriconazole versus 19 patients receiving amphotericin B developed 'renal impairment'. According to additional data on serum creatinine values provided by the sponsor, all these patients experienced at least a two-fold increase in serum creatinine from baseline values.

Wingard 2010: according to a figure in an appendix, 10% of the patients in each group needed dialysis, but this was not described further, or in the main text.

Other adverse effects

Walsh 2002: the number of patients discontinuing therapy due to toxic effects was similar in the two groups (19 on voriconazole versus 23 on liposomal amphotericin B); whereas the number discontinuing due to lack of efficacy was significantly different (22 versus 5), in favour of liposomal amphotericin B. Significantly more patients in the voriconazole group experienced visual disturbances (21.9% versus 0.7%) and visual hallucinations (4.3% versus 0.5%), whereas significantly more patients in the liposomal amphotericin B group experienced dyspnoea (0.7% versus 8.8%) and serum potassium below 2.5 mmol/L (2.4% versus 5.0%).

Herbrecht 2002: significantly fewer patients in the voriconazole group discontinued treatment because of toxic effects compared to amphotericin B, 7% versus 43%. Significantly more patients in the voriconazole group experienced visual disturbances (45% versus 4%) and 7% versus 3% had hallucinations or confusion. Significantly fewer patients in the voriconazole group had chills or fever, 3% versus 25%.

Wingard 2010: in total, 24 patients in the voriconazole group and 30 patients in the fluconazole group died of drug related toxicity. This was not described in the text but in the appendix (figures S1, S2 and S3). Three patients in the voriconazole group were missing from figure S2 in the appendix, with no explanation provided.

DISCUSSION

We found that when amphotericin B was given in a liposomal formulation, it was significantly better than voriconazole (Walsh 2002). When it appeared to have been seriously handicapped by being given in a conventional formulation in a long-term trial without any indication of premedication or replacement of electrolytes including with salt water, it performed significantly worse than voriconazole (Herbrecht 2002). Taken together, these results suggest that amphotericin B is a better drug than voriconazole. One study compared voriconazole to fluconazole for propylaxis of fungal infections in patients undergoing allogeneic stem cell transplantation (Wingard 2010). The study failed to find a difference in terms of fungal free survival or risk of invasive fungal infections.

Walsh 2002 was a non-inferiority trial using a validated composite endpoint as the primary outcome. The trial authors found that voriconazole was inferior to liposomal amphotericin B since the 95% CI for the difference (-10.6% to 1.6%) exceeded the predefined limit for non-inferiority of -10.0%. According to the Food and Drug Administration (FDA) in the USA, an analysis that was in agreement with the analysis plan for the trial showed that voriconazole was significantly inferior to liposomal amphotericin B (CI for the difference -12.0 to -0.1) (Powers 2002). Using either analytical approach voriconazole was inferior, and the Antiviral Drug Products Advisory Committee of the FDA voted against accepting empirical use of voriconazole in neutropenic patients as an indication for this drug.

Nonetheless, the trial authors concluded in their abstract that "Voriconazole is a suitable alternative to amphotericin B preparations". This conclusion is partly based on the lower prevalence of breakthrough fungal infections in the voriconazole group, eight versus 21 (P = 0.02), which is also mentioned in the abstract. However, a conclusion based on a single outcome of the composite endpoint seems contrary to the stated intentions in the methods section of the article, which noted that "Secondary analyses of individual composite end points were exploratory assessments and were not intended to be a primary determination of outcome superiority". Furthermore, the trial authors defined breakthrough fungal infections as those that have been confirmed more than 24 hours post-enrolment. The reason for a 24-hour cut-point to exclude baseline fungal infections from the analysis was not explained. We searched the references provided as justification for this cut-point but could not find any relevant information. We have not seen such a cut-point in any of the more than 70 other trials of antifungal therapy that we have reviewed previously (Gøtzsche 2002a; Gøtzsche 2002b; Johansen 2000; Johansen 2002). In a later study of caspofungin a 48-hour cut-point for the same outcome was used, again without any justification or explanation for this change (Walsh 2004). We believe this arbitrary use of cut-points creates bias. When we included those baseline infections that persisted despite treatment, we found 15 versus 23 infections (P = 0.27). Our analysis is unbiased and it is also clinically relevant as patients with baseline infections are part of the clinical reality when one treats on suspicion of a fungal infection.

Walsh 2002 attributed the significantly higher mortality in the voriconazole group to a higher mortality from progressive cancer (13 versus five patients). However, this cannot explain the entire difference in mortality, which is 17 deaths. Furthermore, it is of note that 15 versus nine patients died from sepsis and seven versus one patient died from bacterial pneumonia since azoles may have an immune suppressing effect and have increased the number of bacterial infections in randomised trials compared to patients receiving no treatment (Gøtzsche 2002b).

The trial was not blinded, which could have influenced the assessment of adverse effects, in particular when the trial authors noted that the voriconazole group had fewer cases of severe infusion related reactions. Furthermore, they did not define what they meant by this or give the number of cases; there is only a P value in the abstract relating to this statement. Without definitions, such a statement is virtually meaningless, for example it is impossible to judge whether 91 versus three cases of abnormal vision are worse or better than 57 versus 126 cases of chills (the trial authors' table 5).

Walsh 2002 found that 29 versus 32 patients had a two-fold increase in serum creatinine. They also found that 43 versus 80 patients experienced a 1.5-fold increase (P < 0.001), which is the result they reported in the abstract. We find this highly misleading. A two-fold increase in serum creatinine has been used in other trials, but we have never seen a 1.5-fold increase and suspect this is an example of data dredging to find something that favoured voriconazole (Johansen 2002). The lack of clinical relevance of the trivial difference in serum creatinine is underlined by the fact that two patients in the voriconazole group and one in the liposomal amphotericin B group died from renal failure. Furthermore, the trial excluded patients with liver affection whereas patients with renal affection were not excluded (Walsh 2002).

Since amphotericin B has little effect on the liver but a potential for nephrotoxicity, and the reverse is true for voriconazole, we believe this creates a bias in favour of voriconazole when assessing nephrotoxic and hepatotoxic effects.

The highly misleading conclusion in the abstract of this trial is undoubtedly very useful for the sponsor's marketing department and it has been quoted by others without provisos (Hughes 2002).

Herbrecht 2002 was flawed by design. Although the planned duration of trial therapy was very long, 84 days, the trial authors used conventional amphotericin B as the control drug and the average duration of therapy was only 10 days in the amphotericin B group compared with 77 days in the voriconazole group. Commentators have pointed out that the high discontinuation rate in the amphotericin B group could have been reduced if the trial authors had used liposomal amphotericin B (Blot 2002; Karthaus 2002). Furthermore, it appeared that the trial authors did not use premedication for prevention of infusion related toxicity, or supplementation with fluid, potassium and magnesium for prevention of nephrotoxicity although these precautions were known to be highly effective when the trial was planned. Such preventive measures have been reported in other trials we have reviewed (Johansen 2000).

One third of the patients in the voriconazole group and 80% in the amphotericin B group received an escape drug, which makes comparisons of adverse effects and other effects in the two groups at the end of the trial period problematic. More patients in the amphotericin B group were switched to itraconazole, the efficacy of which remains debatable in the setting of this trial (Blot 2002). The excess mortality in the amphotericin B group appeared after

10 days of treatment, which coincides with the median duration of therapy in this group (Blot 2002).

Herbrecht 2002 argued that the reason why the liposomal formulation of amphotericin B was not used was that it was not licensed for primary therapy of aspergillosis at the time the trial was planned, and that an improved effect on invasive aspergillosis of the lipid formulation was only speculative and unsupported by any data from the literature. However, well before the trial started in 1997, there was evidence that indicated liposomal amphotericin B was better than the conventional formulation and it had been used early on for *Aspergillus* infections in patients who could not tolerate conventional amphotericin B (Ringdén 1991). In fact, liposomal amphotericin B was licensed in Denmark for use for all of its present indications, including invasive *Aspergillus* infections, on 11 October 1994 (Swedish Orphan, personal communication). It is also curious that liposomal amphotericin B was used as one of the escape drugs, in both groups of the trial, if it was believed to be no better than conventional amphotericin B.

Significantly more patients in the voriconazole group had a definite *Aspergillus* infection at baseline, 67 (47%) versus 41 (31%). We think complete response to therapy is a more clinically relevant outcome than partial response in this long-term trial and 30 (21%) versus 22 (17%) patients responded. This difference is in favour of voriconazole, but if the responses are related to the number of definite diagnoses at baseline fewer patients responded on voriconazole, 30 out of 67 (45%) versus 22 out of 41 (54%).

In their abstract, the trial authors concluded that treatment of patients with invasive aspergillosis with voriconazole leads to better responses with improved survival and fewer severe side effects than initial therapy with amphotericin B. Since amphotericin B appeared to have been seriously handicapped in this trial, we believe the conclusion is misleading and that the evidence provided by this trial is not sufficiently strong to support such a conclusion. As with the trial by Walsh 2002, this conclusion has been quoted uncritically in later scientific work (Imhof 2004).

No significant differences could be demonstrated between patients who were treated prophylactically with either voriconazole or fluconazole after undergoing allogeneic stem cell transplantation for leukaemia or other haematopoietic disorders (Wingard 2010).

The primary endpoint in the study (Wingard 2010) was fungal free survival at day 180, which was similar in the two groups (78% in the voriconazole group and 75% in the fluconazole group). Three groups of patients were permitted to receive the study drugs beyond day 100, through to day 180. It was, however, not described how many patients continued such treatment.

The protocol (Wingard 2010) stated that patients in whom the study drug was prematurely withdrawn were allowed to receive fluconazole as an escape drug, but not other antifungal agents. This is a problem as patients receiving open label fluconazole prophylaxis were included in the analysis as being in the voriconazole group, and it is thus unclear if the benefits or drug toxicities were related to voriconazole or the fluconazole escape therapy. Furthermore, it is stated in table 3 that other antifungal agents, including voriconazole, were used as open label prophylaxis contrary to the study protocol.

The toxic side effects were not well described in the text, but in the appendix, figures S1 and S2 it is stated that 30 patients died from drug related toxicity in the fluconazole group and 24 in the voriconazol group.

Some have been critical that only patients with a low risk of invasive fungal infection were included and therefore the true effect of voriconazole in an actual clinical setting was not assessed compared to fluconazole (Girmenia 2011).

AUTHORS' CONCLUSIONS

Implications for practice

Liposomal amphotericin B is significantly more effective than voriconazole for empirical therapy of neutropenic cancer patients and should be the preferred therapy. For treatment of aspergillosis, there are no trials that have compared voriconazole with amphotericin B given under optimal conditions. When voriconazole was compared to fluconazole for prophylaxis of fungal infections in patients treated with allogeneic stem cell transplantation, they had similar effects.

Implications for research

There is a need for a trial in patients with aspergillosis that compares voriconazole with either a lipid formulation of amphotericin B or with conventional amphotericin B given under optimal conditions, that is with premedication and replacement of electrolytes including using salt water.

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The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Herbrecht 2002

Study characteristics	
Methods	Allocation concealment: Central randomisation, minimisation with four stratification factors Blinding of study: No
Participants	391 patients randomised Excluded: 50 patients excluded from the voriconazole group and 52 patients from the amphothericin B group
Interventions	Voriconazole: Intravenous loading dose of 6 mg/kg twice within the first 24 hours, maintenance dose of 4 mg/kg twice daily for at least seven days, followed by 200 mg orally twice daily Amphothericin B deoxycholate: 1 to 1.5 mg/kg/day intravenously
Outcomes	Total mortality Invasive fungal infections Use of escape drugs Nephrotoxicity Other adverse events
Notes	Follow-up period (days): 84 Support: Pfizer

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	High risk	

Walsh 2002

Study characteristics	
Methods	Allocation concealment: computer-generated randomization with two per block design, 1:1 ratio Blinding of study: No
Participants	871 patients randomised Excluded: 34 Mainly leukaemia, but also other cancer patients and patients receiving bone marrow transplantation
Interventions	Voriconazole: Intravenous loading dose of 6 mg/kg twice within the first 24 hours, maintenance dose of 3 mg/kg twice daily, or 200 mg orally twice daily after at least 3 days of intravenous therapy Liposomal amphotericin B: 3 mg/kg/day intravenously
Outcomes	Total mortality Invasive fungal infections Use of escape drugs Nephrotoxicity Other adverse events
Notes	Follow-up period (days): Median of 7 days in both groups. Non-inferiority trial with composite endpoint Support: Pfizer

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes	High risk	

Wingard 2010

Study characteristics	
Methods	Randomization in a 1:1 ratio in permuted blocks (size not stated).
Participants	600 patients with leukaemia or other haematopoietic disorders receiving allogeneic haematopoietic stem cell transplantation treated prophylactically with either voriconazole or fluconazole.
Interventions	Voriconazole: 200 mg orally twice daily for 100 days. Fluconazole 400 mg once daily for 100 days.
Outcomes	Primary outcome: Fungal free survival at 180 days Secondary outcomes: incidence of invasive fungal infections. Time to invasive fungal infections. Six month and 1 year relapse free survival. Overall survival. Time to and duration of empiric antifungal therapy. Frequency of adverse events. Incidence of acute or chronic graft-versus-host disease

Wingard 2010 *(Continued)*

Notes	The follow-up period was 180 days and 1 year Supported by a grant from the National Institutes of Health and an "unrestricted educational grant" from Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	1:1 permutated blocks, unclear if allocation concealment was obtained
Blinding (performance bias and detection bias) All outcomes	Low risk	The clinician, patient and the data review board were blinded

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ally 2001	All patients had oesophageal candidiasis, which is not an invasive fungal infection according to our inclusion criteria; in addition, 94% of the patients had AIDS

WHAT'S NEW

Date	Event	Description
8 June 2020	Review declared as stable	This Cochrane review is not currently a priority topic area. Previous update 2014 and conclusions not changed.

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 1, 2006

Date	Event	Description
11 February 2015	Amended	Contact details updated.
9 January 2014	New citation required but conclusions have not changed	Expanded from two to three included studies and added new author. One additional study awaits assessment.
9 January 2014	New search has been performed	New search conducted January 2014.
5 February 2008	New search has been performed	Minor update
5 November 2007	New search has been performed	Searches were re-run and no additional trials were found.

Date	Event	Description
14 November 2005	New search has been performed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

HKJ and PCG conceived the project. HKJ, PCG and KJJ contributed to the development of the protocol and the first version of the review. HKJ, KJJ and CSD performed the data extraction. The draft for the updated review (January 2014) was written by CSD and revised by KJJ, HKJ and PCG.

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (for example employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- Copenhagen Hospital Corporation, Denmark

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not report on colonisation as there were no data on this in the included trials, nor on total number of dropouts as the trials were flawed by design, rendering such data meaningless.

INDEX TERMS

Medical Subject Headings (MeSH)

Amphotericin B [adverse effects] [*therapeutic use]; Antifungal Agents [adverse effects] [*therapeutic use]; Aspergillosis [drug therapy]; Fluconazole [adverse effects] [therapeutic use]; Liposomes; Mycoses [*drug therapy] [mortality]; Neoplasms [*complications]; Neutropenia [*drug therapy] [microbiology] [mortality]; Opportunistic Infections [*drug therapy] [microbiology] [mortality]; Pyrimidines [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Triazoles [adverse effects] [*therapeutic use]; Voriconazole

MeSH check words

Humans