

CLINICAL EXPERIENCE WITH LINEZOLID IN INFANTS AND CHILDREN

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Resume. The worldwide spread of multidrug-resistant organisms has required the development of new antimicrobials. Linezolid, the first oxazolidinone, has a broad spectrum of activity against Gram-positive bacteria, including resistant strains. Although approved by the Food and Drug Administration in 2002, the clinical experience with linezolid in the paediatric population is still limited, also given the fact that in most European countries the paediatric use of linezolid is off-label. In this paper we summarize the actual evidence on the clinical use of linezolid in children, including efficacy, safety and tolerability issues. Taking into account the potential bias in comparing heterogeneous clinical trials and reports, the available literature data suggest that linezolid is a safe and effective agent for the treatment of serious Gram-positive bacterial infections in neonates and children. At present, linezolid is reserved for those children who are intolerant to or fail conventional agents. A linezolid-containing regimen can be a valuable option for treating multidrug-resistant and extensively drug-resistant tuberculosis in children as well as disseminated non-tuberculous mycobacterial infections. Given the rare occurrence of serious side effects, careful monitoring of haematological parameters, possible drug interactions and neurological manifestations is recommended in linezolid-treated children, especially in case of prolonged treatments. Appropriate linezolid dosage and hospital infection control measures are essential to avoid the spread of linezolid resistance. Further studies are needed to establish novel paediatric indications for linezolid use and to assess the tolerability of long-term treatments.

Keywords: *oxazolidinones, paediatrics, Gram-positive bacteria, tuberculosis*

КЛІНІЧНИЙ ДОСВІД ЗАСТОСУВАННЯ ЛІНЕЗОЛІДУ У НЕМОВЛЯТ І ДІТЕЙ

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Резюме. Всесвітнє поширення множинної лікарської стійкості мікроорганізмів вимагають розробки нових протимікробних препаратів. Лінезолід, перший з оксазолідинонов, володіє широким спектром активності проти грампозитивних бактерій, в тому числі резистентних штамів. Незважаючи на те, що препарат був офіційно схвалений для застосування Управлінням з контролю за продуктами і ліками (Food and Drug Administration - FDA) в 2002 році, клінічний досвід застосування лінезоліду в педіатричній популяції як і раніше обмежений, особливо з огляду на той факт, що в більшості європейських країн лінезолід в педіатрії використовують не за прямим призначенням. У цій статті ми підсумовуємо фактичні дані про клінічні дослідження із застосуванням лінезоліду у дітей, в тому числі дані по ефективності, безпеки та переносимості. Беручи до уваги потенційну упередженість в порівнянні гетерогенних клінічних випробувань і звітів, наявні в літературі дані дозволяють припустити, що лінезолід є безпечним і ефективним препаратом для лікування серйозних грампозитивних бактеріальних інфекцій у новонароджених та дітей. В даний час лінезолід зарезервований для тих дітей, які мають непереносимість або резистентність до інших антибіотиків. Хіміотерапія з використанням лінезоліду також застосовується при лікуванні туберкульозу у дітей з мульти-резистентністю і розширеною резистентністю. З огляду на рідкісне виникнення серйозних побічних ефектів при застосуванні лінезоліду, необхідний ретельний моніторинг гематологічних параметрів, можливих взаємодій між ліками і неврологічних проявів у дітей, особливо в разі тривалого лікування. Необхідні подальші дослідження для встановлення нових педіатричних показань до застосування лінезоліду та оцінити переносимість тривалого лікування.

Ключові слова: *оксазолідинонов, педіатрія, грам-позитивні бактерії, туберкульоз*

INTRODUCTION

During recent decades, the increasing incidence of infections caused by multidrug-resistant Gram-positive bacteria, especially staphylococci, enterococci and pneumococci, along with the spread in the community of methicillin-resistant *Staphylococcus aureus* (MRSA) have prompted the development of new antibacterial drugs. Linezolid is the first member of a new class of antibiotics, the oxazolidinones. Its mechanism of action involves the inhibition of microbial protein synthesis by preventing the formation of a functional 70S ribosomal initiation complex; this mechanism is class specific, and crossresistance to other antimicrobial agents is generally avoided.

Linezolid exhibits a broad spectrum of activity against Grampositive bacteria, including MRSA and coagulase-negative staphylococci (CoNS), glycopeptide-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae*. It is also active against mycobacterial species, including *Mycobacterium tuberculosis* and *Nocardia* spp. Moreover, beside the intravenous (iv) route, the availability of an oral formulation with excellent bioavailability may reduce the duration of iv treatment and hospital stays. Owing to these properties, linezolid represents a valid alternative to glycopeptides for the treatment of severe infections.

Linezolid was licensed by the FDA in adults and children in 2002; subsequently its use in US children's

hospitals for the treatment of *S. aureus* infections increased substantially. In most European countries linezolid use in the paediatric setting remains off-label, though a recent study in three European countries documented that it is widely prescribed in an age-related manner, along with quinolones and meropenem.

This notwithstanding, the experience with linezolid in paediatric patients is still limited, especially in younger children. To date, most clinical information on its efficacy and tolerability is derived from the adult population.

The aim of this article is to summarize the actual data on both licensed and compassionate clinical uses of linezolid in children, including efficacy, safety and tolerability issues.

METHODS

The Medline, EMBASE and Cochrane library databases were systematically searched through 25 August 2010 to identify all published papers, with at least the abstract in English language, regarding the use of linezolid in infants and children (aged <18 years). The following terms were used for the database search: 'linezolid', 'paediatrics', 'children', 'newborn', 'infant', 'neonate', 'adolescent'. A cross-check on references of major articles was performed as well. To identify ongoing trials or recently completed trials, a search on the WHO trials register was performed.

Pharmacokinetic and pharmacodynamic studies were excluded from the present review.

DOSAGE

Based on the results of clinical trials and manufacturer's instructions, the recommended linezolid dosage is 10 mg/kg three times daily in children up to 11 years of age and 10 mg/kg (maximum dose 600 mg) twice daily in older children. As linezolid clearance is relatively decreased in pre-term (gestational age <34 weeks) as well as term infants, days of age, all neonates should receive a dose of 10 mg/kg twice daily during their first week of life. This dosage can be augmented to 10 mg three times daily in case of inadequate clinical response to the initial dosage. Owing to pharmacokinetic variability, therapeutic drug monitoring (TDM) may be useful in pre-term infants.

COMPLETED CLINICAL TRIALS

Four clinical trials, including 611 children up to 17 years of age treated with linezolid, are available in the literature.

Of the six studies registered on the WHO trial database, four have been completed: their results have been supplied by Pfizer Inc. for informational purposes and synopses are available publicly.

Community-acquired pneumonia

Kaplan et al. investigated safety, tolerability, pharmacokinetics and efficacy of linezolid in a Phase II, open-label, nonrandomized, uncontrolled, multicentre study that enrolled 79 hospitalized children aged 12 months–17 years with community acquired pneumonia (CAP). Intravenous linezolid, followed by oral suspension, was administered at a dose of 10 mg/kg twice daily for a mean of 12.2 days. Sixty-six

children completed treatment and follow-up and were evaluable for clinical outcome. *Streptococcus pneumoniae*, Group A Streptococcus and MRSA were isolated from blood or pleural fluid cultures in eight children. At the follow-up visit, 61 patients [92.4%; 95% confidence interval (CI) 83.2–94.5] were considered cured, 4 were indeterminate and 1 failed. As to safety, in the intent-to-treat (ITT) group, 20 children (25.6%; 95% CI 16.4 to 36.8) had at least one adverse event possibly related to linezolid. The most common adverse effects were diarrhoea (10.3%), neutropenia (6.4%) and elevation in alanine aminotransferase (6.4%).

Resistant Gram-positive infections

Linezolid was compared with vancomycin as to efficacy and safety for the treatment of resistant Gram-positive infections in a Phase III, randomized, open-label, comparator-controlled multicentre trial. Hospitalized children, years of age with nosocomial pneumonia, complicated skin and skin structure infections (cSSSIs), bacteraemia or other systemic infections caused by antibiotic-resistant Gram-positive bacteria were randomized to receive either iv linezolid (10 mg/kg three times daily) or vancomycin for at least 3 days. After 3 days of iv treatment, patients in the linezolid group could be switched to the oral formulation, while those in the vancomycin group could receive an appropriate oral antimicrobial agent, if available. Of the 321 children enrolled, 219 received linezolid and 102 received vancomycin; 168 patients in the linezolid group and 76 in the vancomycin group completed the study. The mean total duration of linezolid treatment was 11.3 days. Clinical cure rates were 79% versus 74% ($P=0.36$) and 89% versus 85% ($P=0.31$) for linezolid and vancomycin in ITT and clinically evaluable patients, respectively. Cure rates were similar by age and infection diagnosis. Pathogen eradication rates in microbiologically evaluable patients were similar for linezolid and vancomycin, respectively, for methicillin-susceptible *S. aureus* (MSSA) (95% versus 94%; $P=0.82$), MRSA (88% versus 90%; $P=0.89$) and methicillin-resistant CoNS (85% versus 83%; $P=0.87$). Among clinically evaluable patients, those receiving linezolid required significantly fewer days of iv therapy than vancomycin-treated patients (8.0+4.8 days compared with 10.9+5.8 days; $P<0.001$). Linezolid-treated patients had fewer drug-related adverse events compared with the vancomycin group (19% versus 34%; $P=0.003$). The most common linezolid-related adverse events were diarrhoea (3.8%), vomiting (1.9%), thrombocytopenia (1.9%) and loose stools (1.9%). Haematological events were uncommon and similar between the two groups.

Bacteraemia and hospital-acquired pneumonia

Results from a subset of children with bacteraemia or hospital-acquired pneumonia (HAP) enrolled in the previously cited Phase III controlled trial were reported by Jantaush et al. Twenty-three out of 39 children with HAP and 81 out of 113 with bacteraemia received linezolid for a mean of 10.5+4.7 days. For clinically evaluable patients with HAP, clinical cure rates were comparable between the linezolid and vancomycin

groups (90% versus 100%; $P=0.305$). It is noteworthy that more patients in the linezolid group compared with the vancomycin group had multiple lobe involvement (90.9% versus 50%; $P=0.038$) and required mechanical ventilation (63.6% versus 10%; $P=0.011$). Clinical cure rates were similar between the two groups in patients with catheter-related bacteraemia (84.8% versus 80.0%, respectively, for linezolid and vancomycin; $P=0.716$) or with bacteraemia of an unknown source (79.2% versus 69.2%, respectively; $P=0.501$). Similar percentages of laboratory alterations, including selected haematological parameters, were observed in both treatment groups.

Complicated skin and skin structure infections

The clinical efficacy and safety of linezolid compared with vancomycin for the treatment of cSSSIs were evaluated in a subgroup of patients belonging to the same Phase III controlled trial. The study analysed 120 ITT patients: 80 received linezolid and 40 vancomycin. *S. aureus* was the most common pathogen isolated at baseline (79.7%). Clinical cure rates were comparable between the two treatment groups in the overall ITT population (86.5% versus 82.4%, respectively, for linezolid and vancomycin; $P=0.574$). Clinically evaluable patients with skin abscesses treated with linezolid had a significantly higher cure rate than those treated with vancomycin (100% versus 60%, $P=0.005$). Pathogen eradication rates were similar between treatment groups, regardless of the pathogen isolated and its pattern of resistance. Significantly fewer linezolid-treated patients had drug-related side effects compared with vancomycin-treated patients (23% versus 48%; $P=0.0059$). The most common linezolid-related adverse effects were diarrhoea (5.1%) and thrombocytopenia (3.8%); metabolic acidosis was observed in two patients (2.5%), but it was considered unrelated to linezolid treatment.

Neonates

Deville et al. performed a subset analysis on the neonatal population included in the Phase III trial described by Kaplan et al. Linezolid was compared with vancomycin for the treatment of resistant Gram-positive infections in 63 neonates: 43 neonates were treated with linezolid and 20 with vancomycin. Infants in the linezolid group were younger, of lower gestational age and of lower post-conception age, although the difference in the baseline characteristics between the two treatment groups was statistically significant only for the post-natal age (25.7 days in the linezolid group versus 40.3 days in the vancomycin group; $P=0.02$). The most common baseline diagnosis in both groups was bacteraemia (57.1%), CoNS being the most frequently isolated pathogen (58%). Cure rates were higher in the linezolid group (77.5% versus 61.1%), although the difference was not statistically significant ($P=0.196$). Pathogen eradication rates in the linezolid group were 88% for CoNS, 67% for MRSA and 71% for enterococci. The efficacy of linezolid against MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE) was comparable to that of vancomycin. Drug-related adverse events were reported in fewer linezolid-treated infants than in vancomycin-treated infants (11.6% versus 31.6%,

$P=0.058$). The percentages of patients with abnormalities in haematology or serum chemistry values were similar in the two groups; however, more linezolid-treated patients had decreased haemoglobin and haematocrit levels and increased total bilirubin.

Uncomplicated skin and skin structure infections

A prospective, randomized, blinded, comparator-controlled, multinational trial compared the efficacy and safety of linezolid and cefadroxil for the treatment of uncomplicated SSSIs in paediatric patients. Children from 5–17 years of age were randomized to receive either oral linezolid (10 mg/kg or 600 mg twice daily according to age) or oral cefadroxil (15 mg/kg or 500 mg twice daily according to age). The study enrolled 508 patients, of whom 248 received linezolid and 251 cefadroxil. Cure rates were similar in the linezolid and cefadroxil groups, both in the ITT population and in clinically evaluable patients (88.7% versus 86.2%, $P=0.405$, and 91.0% versus 90.0%, $P=0.737$, respectively). The most frequently isolated pathogen was *S. aureus*, whose eradication rate was 89.6% in the linezolid group and 88.5% in the cefadroxil group. Gastrointestinal disturbances were the most common adverse events reported in both treatment groups; myelosuppression was not observed. Data from this outpatient trial were compared with data obtained from a previously described inpatient trial to evaluate the clinical efficacy and safety of iv and oral linezolid in children with MRSA infection. In the outpatient trial, the pathogen eradication rate for MRSA was 92.3% in the linezolid group and 85.7% in the cefadroxil group ($P=0.64$). Few drug-related adverse events were reported. In the inpatient trial, pathogen eradication rates were 88.2% and 90.0%, respectively, for the linezolid and vancomycin groups ($P=0.89$). Fewer patients in the linezolid group had drug-related adverse events than in the vancomycin group (20% versus 43%, $P=0.15$).

Acute otitis media

Linezolid was effective for the treatment of acute otitis media in an open-label, uncontrolled Phase II trial involving 65 children (mean age 2.8 years) receiving oral linezolid (10 mg/kg twice daily) for 7–10 days. The most common isolated pathogens were *S. pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Moraxella catarrhalis*. The clinical success rate in clinically evaluable patients was 69.1%. Success rates were greater in the group of children >2 years old compared with younger children, regardless of the pathogen isolated (93.3% versus 42.9%). A better clinical response was reported in children without a previous diagnosis of acute otitis media compared with those with recurrent disease (76.5% versus 50.0%).

Vancomycin-resistant enterococcal infections

The safety, tolerability and clinical efficacy of iv and oral linezolid in children up to 17 years of age with known vancomycin-resistant enterococcus (VRE) infections was evaluated in a randomized, open-label, Phase III study. Of the 13 patients initially enrolled, 10 were clinically and 7 were microbiologically evaluable

(ME). Clinical cure or improvement was achieved at follow-up in 66.7% of patients in the ITT population. Microbiological eradication was achieved in 69.2% and 71.4% of patients, respectively, in the modified intent-to-treat (MITT) and ME populations. Linezolid was well tolerated: most adverse events were rare and the types of events were not unexpected among seriously ill hospitalized paediatric patients.

Community-acquired pneumonia caused by penicillin-resistant *S. pneumoniae*

Linezolid was safe and effective for the treatment of pneumonia caused by penicillin-resistant *S. pneumoniae* (PRSP) in an open-label, non-randomized, uncontrolled, Phase III study. The study enrolled 229 patients aged 14–96 years (ITT population) with CAP and treated with either oral or iv linezolid. All isolates of *S. pneumoniae* were susceptible to linezolid, with MICs ranging from 0.25–2.0 mg/L. A microbiological success (documented or presumed eradication), evaluated in the MITT population, occurred in 84.3% (95% CI 76.7–91.8%) of patients, regardless of the susceptibility pattern of *S. pneumoniae*, and in 87.3% (95% CI 79.1–95.5%), 84.6% (95% CI 65–100%) and 69.2% (95% CI 44.1–94.3%) of patients with penicillin-susceptible, penicillin intermediate and penicillin-resistant *S. pneumoniae*, respectively. At follow-up, the cure rate for MITT patients was 84.3% (95% CI 76.7–91.8%); reclassifying the eight patients with indeterminate clinical outcome as failed, the cure rate was 77.3% (75/97 with 95% CI 69.0–85.7) and the failure rate was 22.7% (22/97). There was no correlation between penicillin susceptibility and clinical outcome. Forty-nine patients (21.4%) had at least one drug-related adverse event. Those reported in more than 2% of the ITT population were nausea (3.1%), diarrhoea (2.6%) glossitis, (2.2%) and localized abdominal pain (2.2%). No subset analysis for the paediatric population was performed.

Catheter-related Gram-positive cSSSIs and bloodstream infections

An open-label, randomized, controlled Phase III trial evaluated the clinical efficacy of linezolid compared with vancomycin/oxacillin/dicloxacillin in the treatment of Gram-positive infections of short-term indwelling vascular catheters. The study population included 739 patients aged ≥ 13 years: a stratified analysis for the paediatric population was not reported and the youngest patient in the linezolid group was 16 years old. Linezolid was as effective as standard therapy for the treatment of cSSSIs related to indwelling catheters and for the treatment of catheter-related bloodstream infections (77.8% versus 77.9% and 75.3% versus 80.0%, respectively). The incidence of serious adverse events was higher in the linezolid group. This study demonstrated that linezolid was not inferior to vancomycin and other control regimens in patients with cSSSIs or catheter-related bloodstream infections due to Gram-positive organisms; however, no specific conclusions can be drawn from this study for the use of linezolid in children.

Febrile neutropenia

A double-blind randomized Phase III study comparing linezolid and vancomycin in the treatment of febrile neutropenic oncology patients with a proven or suspected Gram-positive infection was prematurely discontinued due to slow enrolment and for administrative reasons. The study population included 120 adults and adolescents 15–80 years of age. Although the small number of subjects enrolled does not allow definite conclusions to be drawn, clinical cure rates and the proportions of adverse events were similar among linezolid- and vancomycin-treated subjects. A stratified analysis for the paediatric population was not given, but it can be inferred that among adolescents both the safety and side-effect profile of linezolid were similar to those in adults.

ONGOING CLINICAL TRIALS

Cystic fibrosis

A pharmacokinetic, non-randomized, open-label study is investigating the use of linezolid in children with cystic fibrosis with pulmonary exacerbations and isolation of MRSA in their sputum. Aims of the study are to determine the pharmacokinetic profile of iv and oral formulations of linezolid and to establish a dose regimen that will be safe and effective in children with cystic fibrosis. Linezolid is administered at 15 mg/kg three times daily for 7–28 days.

Secondarily infected traumatic lesions and impetigo due to MRSA

A randomized, double-blind, comparative, Phase III study is comparing retapamulin ointment versus oral linezolid in the treatment of secondarily infected traumatic lesions and impetigo due to MRSA. Subjects aged ≥ 2 months are treated with either topical retapamulin for 5 days or oral linezolid for 10 days. The primary endpoint is the clinical response at follow-up in subjects with a MRSA infection at baseline.

META-ANALYSES

Two recent meta-analyses have evaluated the clinical efficacy of linezolid. It should be emphasized that they included both adult and paediatric studies, but no subanalysis was performed to assess children separately. Falagas et al. assessed 12 randomized controlled trials of linezolid having a glycopeptide or a β -lactam as a comparator. More than 6000 patients with drug-resistant Gram-positive bacterial infections were enrolled. Linezolid proved highly effective for the treatment of skin and soft tissue infections. Conversely, its efficacy was similar to that of comparators as far as pulmonary and bloodstream infections were concerned. Linezolid was associated with higher rates of microbiologically documented eradication of *S. aureus* infections compared with glycopeptides. However, this superiority was not maintained for MRSA and enterococci. The proportion of patients who dropped out of the trials for side effects was similar in the different treatment arms; linezolid was associated with a higher, although not statistically significant, risk of adverse events. The main side effects that caused linezolid-treated patients to drop out of the

trials were gastrointestinal adverse events, followed by haematological alterations. The second meta-analysis evaluated randomized controlled trials comparing linezolid with vancomycin for the treatment of Gram-positive bacterial infections. This meta-analysis did not find any difference between treatments in terms of clinical cure of Gram-positive bacteraemia and pneumonia, whereas better cure rates were obtained by linezolid in the treatment of skin and soft tissue infections. Greater microbiological eradication of MSSA, but not MRSA and enterococci, was observed with linezolid treatment. The frequency of adverse events was comparable between the two treatment groups. The limitations of this meta-analysis have been recognized by the authors, in particular the unblinded nature of the majority of the evaluated trials and the lack of systematic monitoring of vancomycin plasma levels.

CASE SERIES AND CASE REPORTS

A total of 14 case series and 43 case reports were found, including a total of 206 children aged 7 days–17 years (Tables 3 and 4). Use of linezolid in children has been reported for several approved and off-label indications. The most common pathogens against which linezolid has been used are *Staphylococcus spp.* and *Enterococcus spp.* A few interesting cases of unusual pathogen infections (*Nocardia spp.*, *Gemella haemolysans* and mycobacteria) successfully treated with linezolid are available as well.

Respiratory tract infections

Isaacson et al. described a consecutive series of eight children with refractory Gram-positive otorrhoea treated with linezolid. Ten episodes were documented, seven caused by MRSA and three by multidrug-resistant (MDR) *S. pneumoniae*. All children received oral linezolid at 20 mg/kg/day for 14 days, with otorrhoea resolution and no side effects. One child had recurrent infections starting 3 months after completion of linezolid treatment. Clinical and radiological resolution of complicated CAP were obtained in two children treated for 20–23 days with linezolid as a continuous iv infusion at 30 mg/kg/day in combination with imipenem. A 14-year-old girl with MRSA pneumonia was successfully treated with iv linezolid 600 mg/day for 3 weeks and pneumothorax. Conversely, a therapeutic failure was reported in a child with cystic fibrosis and MRSA pneumonia. Multiple prolonged courses of linezolid were administered during the previous 2 years at 10 mg/kg either two or three times daily. The strain was eventually found to be resistant to linezolid but susceptible to vancomycin; a G2576U mutation was identified in domain V of the 23S rRNA.

CNS infections

The rapid penetration of linezolid into CSF suggests a potential use in the treatment of meningitis and intracranial prosthetic device infections. Yilmaz et al. described six paediatric patients with ventriculoperitoneal (VP) shunt infection who received linezolid either for failure of the initial antimicrobial regimen, including vancomycin, or for a VRE infection. Mean age was 11.83 months (range 4–36 months). The mean duration of

linezolid treatment was 18.17 days (range 14–21 days). Four patients were treated with external ventricular drainage. Microbiological sterilization of CSF and clinical cure were achieved in all patients and no side effects were reported.

Several case reports on paediatric nosocomial CNS infections treated with linezolid as second-line treatment have been published.

Four patients aged 7–20 months were successfully treated with iv linezolid 10 mg/kg three times daily for ventriculitis caused by *Enterococcus faecium*; treatment duration was 15–28 days and no adverse events were noted. A 6-week-old child with a VP shunt had meningitis and ventriculitis caused by *E. faecium*: he received iv linezolid 10 mg/kg three times daily for 21 days, then twice daily for 14 days, according to TDM results. CSF sterilization and clinical resolution were achieved without adverse events.

Three other cases of bacterial meningitis in children receiving linezolid have been described: an infant aged 6 months with a CoNS infection that was complicated by subdural empyema, a 17-month-old child with congenital heart disease and meningitis due to *G. haemolysans*, and a 14-year-old child with MRSA infection. A high CSF penetration of linezolid was reported in a 4-year-old child with VP shunt infection caused by *Enterococcus faecalis* and successfully treated with iv linezolid 10 mg/kg three times daily for 10 days.

The remaining linezolid-treated children include a 4-year-old male with developmental delay and seizure disorder and VP infection by MRSA; a 12-year-old kidney transplant recipient with multiple brain abscesses and pneumonia caused by *Nocardia farcinica* who received oral linezolid 600 mg twice daily for 8 weeks and developed anaemia; a subdural empyema caused by *Streptococcus constellatus* in a 15-year-old child treated with linezolid for 38 days; a subdural empyema successfully treated with linezolid and rifampicin in a 4-year-old child with MRSA infection following surgical debulking of a cerebral astrocytoma; a 17-year-old male with brain abscess and sinusitis that were refractory to standard antimicrobial regimens and required surgical drainage; and a 17-year-old immunocompetent patient treated with high-dose meropenem, linezolid, moxifloxacin and fluconazole for a relapsing purulent meningo-encephalitis—the causative agent was finally identified as *Acanthamoeba lenticulata*.

Nocardia infections

The prolonged use of linezolid for the treatment of six patients with *Nocardia spp.* infection, including two children, was described by Moylett et al. Both children, aged 6 and 9 years, had chronic granulomatous disease. The first developed cavitary pneumonia caused by *Nocardia brasiliensis* and received linezolid 10 mg/kg twice daily for a total of 24.5 months. The second child had a disseminated disease, with nasal abscess and bilateral pneumonia, and was treated with oral linezolid 300 mg twice daily for 12 months. Both patients were cured.

Paediatric intensive care patients

In the paediatric intensive care setting, oral linezolid may represent a valid alternative to iv glycopeptides, especially when prolonged iv access is not feasible. A cohort of seven intensive care patients with either MRSA, *S. epidermidis* or *Enterococcus spp.* infection was treated with linezolid for 7–42 days. All children initially received iv vancomycin and then switched to oral linezolid 10 mg/kg twice daily. No side effects were noted.

Osteoarticular infections

Although not approved for such indications, linezolid appears an interesting option for the treatment of acute and chronic osteoarticular infections, given its good bone penetration and the availability of an oral formulation. However, the prolonged duration of antimicrobial treatment required by this type of infection exposes patients to a higher risk of haematological and neurological toxicity. Several observational studies in adults have used linezolid as a single agent or in combination with rifampicin. The overall rate of clinical cure in 198 adults was 80%. A retrospective study comparing the combinations linezolid/ rifampicin versus co-trimoxazole/ rifampicin as oral treatment for bone and joint infections demonstrated similar clinical and safety profiles between the two groups. In the paediatric setting, an observational study by Chen et al. retrospectively collected 13 children aged 3 months– 14 years treated with a linezolid-containing regimen for an osteoarticular infection (with or without bacteraemia). In all children the infection was microbiologically documented and a Gram-positive organism was isolated (MRSA in 11 children, MSSA and *E. faecium* plus CoNS in 1 case each). Linezolid was generally administered as a second-line treatment for failure of previous therapy with conventional antibiotics or intolerance to glycopeptides. The dosage was 10 mg/kg three times daily in children aged < 11 years and 600 mg twice daily in older children, for a median duration of 23 days (range 5–41 days). The overall clinical cure rate, considering that surgical debridement was performed in nine cases, was 84.6%. Despite prolonged treatment, adverse events were rare. Two children developed anaemia, but did not require linezolid suspension; it is worth considering that both children had low baseline haemoglobin levels, a recognized risk factor for linezolid-induced anaemia. Five paediatric case reports of osteoarticular infections successfully treated with linezolid have been published: two spondylodiscitis, two septic arthritis and one mandible osteomyelitis. Infections were caused by *S. pneumoniae* and *S. aureus*; the pathogen was not identified in one case of vertebral osteomyelitis. Linezolid treatment duration ranged from 21 days–1 year. In this group of patients, adverse events were quite often noted. In one patient, bilateral optic neuropathies induced by long-term linezolid were reported; a partial visual recovery occurred after drug discontinuation. A second patient with osteomyelitis suffered from peripheral neuropathy that resolved 10 months after linezolid discontinuation. The child with MRSA polyarthritis and bacteraemia suffered from transient tooth and tongue discolouration.

Enterococcal infections

A retrospective study of 15 hospitalized children with VRE infection and treated with linezolid during a 2 year observation period was conducted in a paediatric hospital in Buenos Aires, Argentina. The median age was 7 years (range 1 month– 15 years) and the median length of treatment was 15 days, with an average hospital stay of 74 days. VRE infection was microbiologically documented in 11 (73.3%) patients and was successfully treated in 13/15 children; two patients died while receiving treatment. Linezolid-related myelosuppression was quite common in this case series (55.5%): leucopenia was reported in three cases, anaemia in two, and thrombocytopenia and neutropenia in one case each. Other reported adverse events were rash (two cases) and elevated liver function tests (LFTs; two cases).

Neonatal infections

Four neonatal case series have been published. Hoehn et al. described two premature infants with *E. faecium* infection (pneumonia and sepsis in the first and necrotizing enterocolitis in the second) successfully treated with iv linezolid 10 mg/kg three times daily for 14 or 16 days. Linezolid was used for the treatment of two additional cases of VRE necrotizing enterocolitis in premature infants (aged 25 and 52 days): clinical cure was reached in both patients and no side effects were recorded. The third case series involved five premature infants with ventriculostomy-related CSF infections after posthaemorrhagic hydrocephalus. The mean gestational age was 26.4+1.1 weeks and the mean birth weight was 910.2+223.5 g. The causative agent was *S. epidermidis* in three cases and *E. faecalis* and *Staphylococcus haemolyticus* in one case each. All neonates received linezolid 10–15 mg/kg three times daily as part of their antibiotic regimen for a mean of 20.8+10.6 days and were microbiologically and clinically cured. CSF penetration of linezolid was good. Three premature neonates were treated with linezolid for enterococcal bloodstream infection (BSI) with or without meningitis in the setting of a VRE outbreak in a neonatal intensive care unit (NICU) in Jerusalem, Israel. The mean gestational age was 30.7+0.6 weeks and the mean birth weight was 821.7+307.7 g. The duration of linezolid treatment was 12–21 days and no abnormalities in complete blood counts or liver enzymes were noted. All neonates recovered fully after treatment, but in one case stool cultures remained positive for VRE throughout hospitalization.

Oncology patients

A prospective non-comparative unblinded study was conducted in a haemato-oncology unit in Athens, Greece, over a 2 year period. Linezolid at 10 mg/kg three times daily was intravenously administered as monotherapy during chemotherapy cycles to 17 immunocompromised children aged 6 months– 11 years with cancer. Ten patients had bacteraemia caused by either MRSA, VRE or *S. pneumoniae* and seven had fever and VRE colonization. The mean duration of linezolid administration was 12.2 days (range 6–38 days). All patients were clinically cured at the end of treatment. The overall rate of adverse events was 23.5%;

no premature discontinuation of linezolid occurred. Four patients had thrombocytopenia and two had anaemia, however, chemotherapy-induced myelotoxicity was not worsened by linezolid administration.

Hospitalized patients (miscellaneous)

The preliminary results of a multicentre study by the Italian Society for Paediatric Infectious Diseases were recently presented. Fifty-two hospitalized children aged 7 days–16 years who received linezolid for a suspected or proven Gram-positive or mycobacterial infection were analysed retrospectively. The conditions requiring linezolid administration were osteoarticular infections, pneumonia, CNS infections, cSSSIs, BSIs, endocarditis and tuberculosis. Mean linezolid treatment duration was 28 days. The most frequent adverse events were diarrhoea (9.6%) and vomiting (7.8%). Two patients had severe anaemia requiring linezolid discontinuation and one had thrombocytopenia. Two patients had grade 3 LFT elevations; one had pancreatitis. Clinical cure was achieved in 36/52 patients, clinical improvement in 15 and failure in 1.

Endocarditis

Linezolid has been used in five paediatric cases of endocarditis, including two pre-term infants. A 4-month-old, 26-week premature infant with a central venous catheter developed tricuspid valve endocarditis caused by VRE. He was successfully treated with linezolid, first intravenously (7 weeks) and then orally (2 weeks). The second case was a 28-week premature infant who developed an indwelling venous catheter-associated right atrium endocarditis caused by MRSA. Unresponsive to previously administered antibiotics, he received iv linezolid treatment at 10 mg/kg three times daily: after 10 days, blood cultures were sterile and an echocardiogram demonstrated a decreased mass. The patient died some days later of heart failure. A 2-year-old child with mitral valve endocarditis due to multidrug-resistant *Streptococcus mitis* received linezolid at 10 mg/kg three times daily for 8 weeks. He developed progressive anaemia, but recovered 19 days after cessation of linezolid. The remaining two children, aged 5 and 4 years, with complicated congenital heart disease, developed MRSA bacteraemia and endocarditis (of the pulmonary and tricuspid valve, respectively) following cardiac surgery. In the first child, the MRSA strain was found to have reduced susceptibility to vancomycin. Both patients were successfully treated with linezolid for 8 and 5 weeks, respectively. During linezolid treatment the 4-year-old patient developed anaemia (haemoglobin – 5.3 g/dL) and thrombocytopenia (platelets – 14–103/mL) requiring blood and platelet transfusions: both resolved after linezolid discontinuation.

Sepsis and bacteraemia

Three children, including two premature infants, with sepsis and bacteraemia were successfully treated with linezolid at a dosage of 10 mg/kg three times daily for 14–21 days. The pathogens isolated were MRSA, *Staphylococcus capitis* and *S. epidermidis* in one case each. The systemic infusion of linezolid was combined

with an 8 h central venous catheter (CVC) lock with linezolid at 2 mg/mL and heparin 100 U in a 4-year-old girl with cystic fibrosis and short bowel syndrome suffering from recurrent CVC-related *S. epidermidis* bacteraemia. As CVC removal was deemed not feasible in this case (although recognized as strongly recommended), a salvage therapy was attempted: systemic and local linezolid was administered for a total of 20 days without side effects. Blood cultures were negative after 2 days of treatment and the CVC was retained. Irreversible auditory nerve neuropathy was found in a 22-day-old, 30-week premature infant treated with linezolid for 14 days for MRSA sepsis. He had respiratory distress syndrome at birth and had received vancomycin plus gentamicin since the fifth day of life; the plasma levels of both antibiotics were within normal ranges.

Skin and skin structure infections

Two cases of SSSIs treated with linezolid have been reported. Linezolid was successfully administered for 28 days in an 11-year-old HIV-positive child with cellulitis of the toe. Tooth discolouration was reported. A 16-year-old boy with an acute flare of Crohn's disease and perirectal abscess responded to linezolid as a third-line regimen, having developed a ciprofloxacin-induced QT interval prolongation.

Community-acquired MRSA Infections

Two cases of community-acquired MRSA (CA-MRSA) infection in linezolid-treated children have been reported in the literature, the first being an adolescent with bacteraemia, epidural abscess, multiple pulmonary abscesses and multiple pneumothoraces, and the second being a 15-year-old child with a severe invasive infection (meningitis, bacteraemia, necrotizing pneumonia and deep vein thrombosis). Clinical success was documented in both cases.

Mycobacterial infections

It has been demonstrated that linezolid has activity against mycobacterial species, including *Mycobacterium fortuitum*, *Mycobacterium chelonae* and *Mycobacterium tuberculosis*. The spread of MDR and extensively drug-resistant (XDR) strains of *M. tuberculosis* has prompted a need for new and effective drugs. In this setting, linezolid may be an important option for the treatment of MDR and XDR tuberculosis (TB), although its prolonged use is hampered by side effects. Early adult studies on the use of a linezolid-containing regimen to treat MDR-TB demonstrated a rapid sterilization of mycobacteria with the standard dosage (600 mg twice daily), although myelosuppression and neurotoxicity were frequently observed. Later studies suggested that a reduced linezolid dose (600 mg once daily) may be equally effective, while reducing the incidence of severe side effects.

A few paediatric cases of TB treated with a linezolid-containing regimen have been published.

A 17-year-old girl with relapsing bilateral pulmonary MDR-TB was unsuccessfully treated in the previous 10 years with various anti-TB regimens. The *Mycobacterium* strain isolated was resistant to eight drugs. She was then given linezolid in combination with capreomycin,

levofloxacin, rifabutin and roxithromycin. Sputum cultures were negative after 5 months of linezolid treatment, but the patient died 8 months later from severe respiratory failure.

A 10-year-old female with HIV/hepatitis B virus (HBV) co-infection developed a disseminated XDR-TB, involving the lungs, pericardium and peritoneum. She was treated with linezolid 800 mg/day in association with pyrazinamide, capreomycin, ethionamide, levofloxacin, imipenem and interferon- γ . She underwent surgery for TB disease and completed a 27 month course of medical treatment. During treatment she developed peripheral neuropathy and anaemia.

Another 10-year-old HIV-positive female had pulmonary XDR-TB and pericarditis with tamponade, requiring pericardiectomy. Oral linezolid at 600 mg/day was administered in combination with imipenem, capreomycin, levofloxacin, ethionamide, pyrazinamide, ethambutol and interferon- γ aerosol for 24 months. No side effects were reported and no evidence of recurrence was noted at the latest follow-up.

Finally, oral linezolid was successfully administered for 19 months to a 4-month-old infant with XDR-TB in association with amoxicillin/clavulanate, capreomycin, clarithromycin, ethambutol, ethionamide, pyrazinamide and terizidone. A case of atypical mycobacterial infection treated with linezolid has also been reported.

A 13-year-old female with sickle cell anaemia had a CVC-related bacteraemia due to *M. fortuitum* resistant to doxycycline and with intermediate susceptibility to clarithromycin. A linezolid-containing regimen was administered with sterilization of blood cultures. Linezolid was discontinued after 2 months because of development of lactic acidosis.

RESISTANCE

Linezolid resistance is rare, with rates lower than 0.1%, and it is mediated by mutations in domain V of the 23S ribosomal RNA gene. Several cases of infections due to linezolid-resistant pathogens have been reported in children. The development of resistance in these patients is likely to have resulted from prolonged administration of a suboptimal dose of linezolid.

Two sisters with hyper-IgE (Job) syndrome and MRSA-related skin disease under suppressive treatment with low-dose linezolid developed a linezolid-resistant strain. Molecular typing suggested transmission of the resistant strain between them. A linezolid-susceptible *S. aureus* was isolated 2 months after linezolid discontinuation. The emergence of linezolid resistance in two isolates of sequence type 36 MRSA was documented in two paediatric patients with cystic fibrosis after long-term low-dose linezolid treatment (300 mg twice daily). Another linezolid-resistant *S. aureus* strain was isolated in a child with cystic fibrosis and pneumonia: a G2576U mutation was identified in domain V of the 23S rRNA. The patient had received multiple prolonged courses of linezolid during the previous 2 years.

A 6-year-old child with severe congenital neutropenia had recurrent bacterial infections and carriage of vancomycin-resistant enterococci. The patient had four courses of linezolid to treat MRSA and VRE

infections before undergoing unrelated donor stem cell transplantation. Resistance to linezolid emerged in the colonizing VRE after each course of this antibiotic when enterococci were present in overgrowth in the gut before treatment.

A fatal sepsis caused by *E. faecium* resistant to glycopeptides and linezolid occurred in an 11-year-old child who underwent haematopoietic stem cell transplantation for β -thalassaemia major. At the time of isolation of linezolid-resistant *E. faecium* from blood, pharyngeal and nasal swabs, the patient was being treated with linezolid, levofloxacin, meropenem, voriconazole and caspofungin. Colonization by the same clone was documented in another child admitted to the same transplant unit and never treated with linezolid. Another linezolid-resistant isolate was documented in an 11-month-old boy who had never received linezolid.

These cases underline the importance of adequate hospital infection control measures, especially when a multiresistant organism is isolated. Moreover, caution is needed in the intermittent use of linezolid in such patients in whom pharmacokinetics is not yet well defined.

SAFETY AND TOLERABILITY IN PAEDIATRIC PATIENTS

Post-marketing studies in adults demonstrated that the prolonged use of linezolid can be associated with myelotoxicity (predominantly thrombocytopenia, less frequently anaemia or pancytopenia), optic and peripheral neuropathy and lactic acidosis due to mitochondrial toxicity. Monitoring the haematological parameters is generally recommended during linezolid administration. Different from haematological abnormalities, which are reversible upon linezolid discontinuation, linezolid-induced neuropathy can become chronic and irreversible. Therefore neurological and ophthalmological evaluations are mandatory in case of prolonged treatments.

In children, both haematological and neurological side effects are less common than in adults. This difference may be partially accounted for by a reduced susceptibility of children to mitochondrial toxicity and a less frequent need for long-term treatments. According to a meta-analysis combining data from four Phase III trials, the most frequent adverse events reported in linezolid-treated children were gastrointestinal disturbances, such as diarrhoea or nausea (7.8%–16.8%), headache (0–6.5%), and vomiting (2.9%–11.9%), followed by skin rash and transient elevation in alanine aminotransferase. None of the common or drug-related adverse events occurred more frequently in patients treated with linezolid than in those in the comparator group. Reversible myelosuppression has been reported in up to 6.4% of paediatric cases. Meissner et al. evaluated the occurrence of haematological effects in children with Gram-positive infections enrolled in an open-label study of linezolid versus vancomycin. Three hundred and sixteen children were randomized to receive either linezolid or vancomycin treatment. No significant differences in haematological profiles between the treatment groups were noted. In the linezolid group, thrombocytopenia occurred in 1.9% of patients, anaemia in 1.4% and neutropenia in none. Four cases of

peripheral and optic neuropathy in children have been reported thus far.

Being a reversible, non-selective inhibitor of monoamine oxidase, linezolid may interfere with other medications acting on the serotonergic and adrenergic system, such as selective serotonin reuptake inhibitors and tricyclic antidepressants: the result may be an increased adrenergic or serotonergic effect, with changes in mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination and fever. A single case of serotonin syndrome has been described in a 4-year-old burn patient with a suspected Gram-positive infection receiving linezolid and fentanyl. Both medications were discontinued and the symptoms gradually resolved.

Two additional cases of potential drug interactions in children have been reported. A 17-year-old neutropenic boy with T cell acute lymphoblastic leukaemia received linezolid for a VRE bacteraemia and concomitant lorazepam for anxiety. The second case was a 7-year-old boy with attention deficit/hyperactivity disorder and major depression receiving linezolid for upper extremity chronic osteomyelitis and concomitant treatment with venlafaxine and methylphenidate. In both cases, concerns for possible interactions between linezolid and psychiatric drugs were raised and the patients were closely followed by psychiatry personnel.

Reversible tooth and tongue discolouration following linezolid treatment have been occasionally reported.

CONCLUSIONS

In the last few decades, the increasing incidence of nosocomial infections caused by multiresistant bacteria has been coupled with the widespread emergence of infections caused by CA-MRSA among previously healthy individuals. The reported prevalence of CA-MRSA varies from 12%–21%. Children and adolescents are at particularly high risk for CA-MRSA infections, given the pattern of antibiotic use in the paediatric setting and the increased use of day care. Approximately 35%–50% of staphylococcal strains in children are community acquired. Linezolid is likely to have an increasing role in children for the treatment of drug-

resistant Gram-positive infections and its expanding use will probably result in a widening of the current indications. Linezolid displays several characteristics that make it a valid alternative to glycopeptides. High and rapid CSF and osteoarticular penetration support its use for the treatment of CNS and osteoarticular infections. The use of oral linezolid avoids the need for long-term iv access and can be useful in step-down therapy in patients requiring relatively long treatments or with intolerance to glycopeptides. In addition, the oral formulation of linezolid provides a definite economic advantage, allowing earlier hospital discharge and reduced costs of outpatient care. On the other hand, concerns have been raised about possible haematological and neurological adverse events. Careful monitoring of haematological parameters, possible drug interactions and neurological manifestations are recommended in linezolid-treated children, especially in case of prolonged treatments. The emergence of linezolid resistance, although still rare, is a matter of concern. The emergence of resistance is often associated with administration of low doses of linezolid, leading to sub-MIC concentrations. This is of particular concern in children, where different age groups require different dosing and pharmacokinetics are not yet well defined. Therefore, appropriate linezolid dosage and hospital infection control measures are essential to avoid the spread of resistant strains. The heterogeneity of available clinical trials and case reports and the limited number of properly conducted randomized double-blind controlled trials may have led to a potentially biased interpretation of these data by the authors of this review and limit our ability to draw definite conclusions. However, from the available literature, linezolid appears safe and effective in children with serious Gram-positive bacterial infections for both approved and off-label indications. At present, linezolid is mainly reserved for children who are intolerant of or fail conventional agents. A linezolid-containing regimen can be a valuable option for treating MDR- and XDR-TB in infancy and childhood, as well as disseminated non-tuberculous mycobacterial infections. Further studies are needed to establish novel paediatric indications for linezolid use and to assess the tolerability of long-term treatments.