Moxifloxacin for the treatment of pulmonary tuberculosis in children: A single center experience

Moxifloxacin for the treatment of pulmonary tuberculosis in children: A single center experience

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Abstract

Objective

To report our experience on the safety and tolerability of moxifloxacin for treating children affected by pulmonary TB.

Study Design

Children receiving a moxifloxacin-containing anti-TB regimen were included in the study. Their medical records were revised at the end of follow-up.

Methods

We describe nine children treated with moxifloxacin for pulmonary TB at Regina Margherita Children's Hospital (Turin, Italy) between 2007 and 2012. Moxifloxacin was administered orally at 10 mg/kg/day once daily (maximum dose = 400 mg/day) following World Health Organization indications. During treatment, patients were systematically assessed for the development of side effects.

Results

Eight children were considered cured at the end of treatment; one child was lost to follow-up after 3 months of treatment. Two children had side effects during treatment: one developed arthritis of the ankle; the other had liver toxicity, whose relationship with moxifloxacin could not be ruled out. We did not observe any case of QT prolongation, central nervous system disorders, growth defects or gastrointestinal disturbances.

Conclusions

A moxifloxacin-containing regimen might be considered for the treatment of TB in children, especially for drug-resistant and extensive forms. However, vigilance for possible side effects is recommended, especially if other drugs are concomitantly used. Studies on wider populations are needed to better define the impact of long-term treatments with quinolones on children's growth and psychomotor development and to outline regulatory indications on moxifloxacin use in the pediatric setting.

INTRODUCTION

Tuberculosis (TB) is a worldwide public health problem both in adults and in children. In industrialized countries, the epidemiology of TB has substantially changed over the last few decades, partly due to migration flows, with young immigrants from TB-endemic low-income countries being the most affected population. With an increasing number of new TB cases in young adults, especially among women of childbearing age, the incidence of TB in children has increased.[**1**] An additional emerging problem is the spread of *Mycobacterium tuberculosis* strains that are resistant to one or more anti-TB drugs.[**2**] In particular, strains resistant to both isoniazid and rifampin, defined as multidrug-resistant (MDR), are associated to an increased risk of treatment failure, further development of drug resistance and enhanced attributable mortality.[**3**] In Italy, the national surveillance system for TB reported in 2008 that 3.7% of strains were MDR, mainly isolated from patients between 15 and 34 years of age.[**4**]

The inclusion in the anti-TB regimen of a later generation fluoroquinolone, such as levofloxacin or moxifloxacin, is recommended to treat isoniazid-resistant, rifampin-resistant, or MDR-TB.[**3**] Indeed, the newer fluoroquinolones have improved pharmacokinetic properties compared with the older ones, in terms of longer serum half-life, higher peak levels, maximal bacterial killing, large volumes of distribution, and extensive tissue penetration.[**5-7**] On the contrary, ciprofloxacin is no longer recommended to treat patients with TB.[**8**]

A fluoroquinolone-containing anti-TB regimen is also considered for pediatric patients with drug-resistant TB, albeit not licensed in this setting.[**9-13**]

Moxifloxacin is a powerful second line anti-TB drug with some favorable properties, including a rapid sterilization activity on mycobacteria, low minimum inhibitory concentrations, readily achieved high peak levels in respiratory tissue and a once-daily administration.[**5, 6, 14, 15**] At present, clinical data on its use in children are scanty, especially for TB patients. In general, quinolone use in pediatrics has been limited following the observation of arthrotoxicity in juvenile animals and is now mainly reserved for serious life-threatening infections for which alternative antibiotic therapies are not effective or available.[**16, 17**] The approved use of quinolones in children is limited to ciprofloxacin in specific situations, such as acute pulmonary exacerbations due to *Pseudomonas aeruginosa* in cystic fibrosis or complicated urinary tract infections.[**18, 19**] Few reports on the pediatric use of quinolones other than ciprofloxacin have been published, though providing encouraging efficacy and safety data.[**1, 19-21**]

Aim of this series is to report our experience on the safety and tolerability of moxifloxacin for treating children affected by pulmonary TB.

MATERIALS AND METHODS

We describe nine children treated with a moxifloxacin-containing anti-TB regimen at our Center (Regina Margherita Children's Hospital, University of Turin, Turin, Italy) between 2007 and 2012.

Moxifloxacin was administered orally at 10 mg/kg/day once daily (maximum dose = 400 mg/day) following World Health Organization indications.[**10**] When necessary, individualized doses were extemporaneously prepared at the pharmacy by crushing moxifloxacin tablets into powder. Patients were prospectively followed during treatment and systematically assessed for the development of side effects. ECGs were performed at baseline and monthly during treatment to monitor potential QT prolongation, along with clinical evaluation, growth assessment and laboratory testing including complete blood count and liver functionality tests.

Diagnosis of pulmonary TB was made on the basis of epidemiological, clinical, and radiological findings, in accordance with World Health Organization criteria.[**10**] In all children at least three samples either of sputum or gastric aspirate were collected before treatment, at the end of the initial phase and before stopping therapy, in order to monitor treatment response.

On each sample, the following tests were performed: microscopy for acid-fast bacilli (AFB) identification, culture on solid and automated liquid medium (BACTEC MGIT 960, Becton Dickinson, Franklin Lakes, NJ) and Nucleic Acid Amplification Tests with a commercial real-time PCR (MTB Q-PCR Alert, Nanogen, Advanced Diagnostics, Buttigliera Alta, Italy) for rapid identification of *M. tuberculosis*. Mycobacteria isolated from culture were identified with the molecular line probe assay GenoType MTBC (Hain LifeScience, Nehren, Germany). Pending culture results, rapid drug susceptibility testing (DST) of isoniazid and rifampin was performed with the molecular line probe assay GenoType MTBDRplus (Hain LifeScience) that identifies mutations in the rpoB gene for rifampin resistance, in the katG gene for high-level isoniazid resistance and in the inhA gene for low-level isoniazid resistance. In vitro DST to first-line drugs was performed using the resistance ratio method with the automated BACTEC MGIT 960 system (Becton Dickinson) with the following final drug concentrations: 1.0 and 6.0 μg/ml for streptomycin, 0.1 and 0.4 μg/ml for isoniazid, 1.0 μg/ml for rifampin, and 5.0 and 7.5 μg/ml for ethambutol (EMB). Susceptibility testing for pyrazinamide, using a modified broth at pH 5.9, was performed with a final drug concentration of 100 μg/ml. In case of resistant strains, second-line drugs susceptibility was tested with the same method at concentrations of 1.0 μg/ml for amikacin and linezolid, 2.5 μg/ml for moxifloxacin and capreomycin, and 5.0 μg/ml for ethionamide.

A patient was defined as cured at the end of treatment when all the following clinical, microbiological, and radiological criteria were satisfied: absence of signs and symptoms attributable to TB, at least three consecutive culture-negative respiratory samples during treatment, chest X-rays normalization.

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and National and Institutional standards. Parental written consent and permission of the local institutional review board for the individual off-label use of moxifloxacin and for collecting data for scientific purposes were obtained.

RESULTS

Nine children, aged 6 months to 13 years, received moxifloxacin as part of their TB treatment. Demographic, clinical, and microbiological data are summarized in Table 1.

Table 1. Demographic, Clinical and Microbiological Characteristics of Children Treated With Moxifloxacin

Patient number	Sex	Age at diagnosis	HIV status	Culture results at baseline	Resistance of TB strain	Total duration of TB treatment (months)	Duration of therapy with MXF (months)
1	M	10 months	N	Positivea	INH, RIF, EMB, PZA, STR	3.0	3.0
2	F	15 months	N	Positivea	INH, STR	7.0	5.7
3	M	6 months	N	Negativeb	INH	7.7	7.4

. N, negative; INH, isoniazid; RIF, rifampin; EMB, ethambutol; PZA, pyrazinamide; STR, streptomycin; para-aminosalicylic acid; CPR, ciprofloxacin.

. aConfirmed drug-resistant TB.
. bPresumed drug-resistant TB.
. cPresumed drug-susceptible TB.

4	M	13 years	N	Positivea	RIF, STR	13.2	12.0
5	F	3 years	N	Negativeb	RIF	9.0	8.5
6	F	6 years	N	Negativeb	INH, STR	7.5	4.0
7	F	6 years	N	Positivea	INH	7.7	3.4
8	F	20 months	N	Positivea	INH, STR EMB, PRZ, RIF	16.0	13.4
9	F	6 year	N	Negativec	None	6.8	4.0

Moxifloxacin was prescribed due to the evidence of pulmonary drug-resistant TB (two MDR, one rifampin and streptomycin resistant, one isoniazid and streptomycin resistant and one isoniazid resistant-TB). One child (# 9) received moxifloxacin, even if affected by a presumed drug-susceptible TB, following a severe adverse reaction to isoniazid: she had vomiting, fever, shaking chills, and hypotension about 1 hr after the intake of the first two doses of isoniazid, after which the drug was discontinued.

Five patients had AFB-positive cultures from sputum or gastric aspirates, on which DST was performed. Four children had repeatedly culture-negative respiratory samples (Table 1): in three of these patients drug resistance was presumed and treatment choice was directed by the DST of the source case (mother, father, and uncle, respectively, all with confirmed drug-resistant TB). In culture-positive patients all strains of *M. tuberculosis* were susceptible to moxifloxacin. In children suspected of having drug-resistant TB, the second line treatment was empirically started pending DST of second-line drugs and then modified according to DST results. The mean ± SD overall duration of the anti-TB treatment was 8.7 ± 3.8 months. Mean ± SD moxifloxacin administration was 6.8 ± 3.8 months.

Children with isoniazid-resistant TB were treated for more than 6 months (mean 7.5, range 7–7.7 months) as recommended.[**3**]

Two children had rifampin-resistant TB, for which the recommended treatment duration is 12–15 months.[**3**] One patient with presumed rifampin resistance had to prematurely discontinue treatment because of liver toxicity (see above); at that time the child was asymptomatic, gastric aspirates were negative and chest X-rays had been unremarkable since 4 months. A strict follow-up of the patient was conducted for the following 36 months.
Of the two children with MDR-TB, one was lost to follow-up after 3 months of treatment; his chest X-ray showed a clear improvement of lung lesions after 2 months of therapy. The second child, with an early primary pulmonary TB, received 16 months of therapy: the treatment duration was guided by the rapid clinical, microbiological, and radiological response of the patient (all findings normalized after 2 months of treatment) and by recent literature supporting shorter (12–15 months) courses of therapy than what advised by WHO in selected pediatric patients.[**22, 23**] The baby was strictly monitored by clinical and radiological assessments and repeated gastric aspirates after treatment completion.
In the five culture-positive patients, gastric aspirates and sputum samples were negative at microscopy, culture and molecular-line probe assays after about 2 months of treatment, and a chest X-ray showed complete healing at the end of treatment. In conclusion, all children were considered cured at the end of treatment, with the exception of the child lost to follow-up.

Two children had side effects during treatment with moxifloxacin. One patient (# 5) had a grade three elevation of liver function tests after 9 months of treatment, at which point treatment was stopped. We recorded one case of arthritis of the ankle (patient #7) that appeared after 3 months of therapy with moxifloxacin; the symptoms spontaneously resolved few days after drug cessation. We did not observe any case of QT prolongation, central nervous system disorders, growth defects or gastrointestinal disturbances.

The mean ± SD follow-up after treatment completion was 25.3 ± 9.5 months. During this period, no cases of relapse and no late-onset side effects attributable to anti-TB drugs, in particular to moxifloxacin, were recorded.

DISCUSSION

The role of later generation fluoroquinolones as second line agents in the treatment of drug-resistant TB has been widely recognized and an in vitro synergy with other anti-tuberculous drugs has been reported.[**24, 25**] Moxifloxacin is increasingly used in adults as a second-line drug in the treatment of drug-resistant TB and a phase 3 trial evaluating the efficacy of a shortened first-line regimen including moxifloxacin for the treatment of drug-susceptible TB is also underway.[**26**] Compared to other quinolones, moxifloxacin has enhanced anti-mycobacterial activity, less potential of selecting resistance and obtained improved outcomes in patients with extensively drug-resistant TB.[**27**] It exerts concentration-dependent killing and has a favorable

pharmacokinetic/pharmacodynamic profile, with sustained plasmatic and intracellular levels.[**5**]

Despite its increasing use in adults, the clinical experience with moxifloxacin in children is limited and reports on its use for TB in children remain anecdotal. This partly comes from a restricted use of quinolonones in pediatrics because of their potential to induce cartilage toxicity.[**19**] Fluoroquinolones-induced arthralgia and/or arthritis is observed especially in adolescents treated with pefloxacin and, to a lesser extent, in children with cystic fibrosis receiving high doses of ciprofloxacin for long periods.[**1**] A case of severe, acute polyarthritis, associated with high doses of oral moxifloxacin, was recently documented in a 12-year-old child.[**28**] In our series, albeit limited, we observed one arthritis of the ankle in a child treated with moxifloxacin for 3 months: signs and symptoms of arthritis were mild and spontaneously resolved upon drug cessation. Liver toxicity was recorded in another patient, though it could not be certainly attributed to moxifloxacin as other hepatotoxic drugs were concomitantly used. Although the follow-up was relatively short, no impact on children's growth and psychomotor development was noticed. Treated patients showed a good response to various TB-combination therapies including moxifloxacin: with the exception of the child lost to follow-up, all children were radiologically and clinically cured at the end of treatment and all previously culture-positive patients became negative within 2 months of starting treatment.

In conclusion, a moxifloxacin-containing regimen might be considered for the treatment of TB in children, especially in drug-resistant and extensive forms were an aggressive and prolonged treatment is needed. However, a strict vigilance in monitoring possible side effects is required. Further studies on different populations are needed to better define the impact of long-term treatments with quinolones in infants and children and to outline regulatory indications on their use in the pediatric setting.

Ancillary

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