

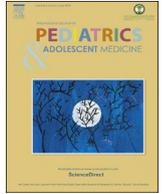
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Original article

Safety and tolerability of moxifloxacin for the treatment of disseminated BCGitis in children

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ABSTRACT

Background and objective: Disseminated BCGitis is a rare but serious complication of BCG vaccine in patients with underlying primary immunodeficiency. Fluoroquinolone antibiotics containing antimycobacterial regimen have been considered in the treatment of disseminated BCGitis, but there are limited data about the dosing, safety, and tolerability of fluoroquinolone such as moxifloxacin in children. The aim of this study was to report the experience with the dosing, safety, and tolerability of moxifloxacin in children with disseminated BCGitis.

Method: This retrospective descriptive study included children who had been diagnosed with disseminated BCGitis and treated with an antimycobacterial regimen including moxifloxacin for more than two weeks from 2007 to 2017 at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Result: Ten children were included: six (60.0%) were male and four (40.0%) were female. The primary diagnosis for five patients was Mendelian susceptibility to mycobacterial diseases (MSMD), four patients were diagnosed with severe combined immune deficiency (SCID), and the remaining patient had human immunodeficiency virus (HIV) infection. The overall mean duration of moxifloxacin treatment was 10.1 months. Liver toxicity was recorded in three patients. The most common medications used with moxifloxacin were ethambutol and clarithromycin. Moxifloxacin serum concentration level was determined in 5 patients. No musculoskeletal side effects were reported while the patient was on moxifloxacin. The treated patients showed a different response to an antimycobacterial regimen including moxifloxacin, with mortality in two patients.

Conclusion: Our study suggests that moxifloxacin is generally tolerated in children and might be considered in disseminated BCGitis cases. Additionally, paying attention to side effects such as liver toxicity is recommended, particularly with the use of other antimycobacterial antibiotics, which could also be hepatotoxic. A moxifloxacin-containing regimen for disseminated BCGitis showed clinical improvement in some patients in this study, although the majority presented the same clinical condition.

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1. Introduction

Disseminated BCGitis is a BCG infection involving any site of the body beyond the vaccination site and ipsilateral lymph node. It is a life-threatening and fatal complication of BCG vaccine in immunocompromised patients such as those with primary immunodeficiency and human immunodeficiency virus (HIV) infection [1]. The complications appear to be early and severe in combined

immune deficiency (SCID), and Mendelian susceptibility to mycobacterial disease (MSMD) compared to those occurring in other primary immunodeficiency diseases. The presence of BCG infection could be the sign to diagnose the underlying immunodeficiency [2]. Rarely, disseminated BCGitis may occur after intravesical instillation of BCG in adult patients with superficial bladder cancer when it is given as adjunctive therapy [3].

BCG vaccine contains attenuated *Mycobacterium bovis*, and it has been used worldwide to confer protection against tuberculosis (TB). The protective efficacy of the vaccine is controversial, with wide variability from 0 to 80% in different trials. In Saudi Arabia, BCG vaccine is administered to all newborns at birth as a part of the national vaccination program since 1970. BCG strains have different susceptibilities to antimycobacterial antibiotics. However, *M. bovis* is known to be intrinsically resistant to pyrazinamide. The incidence of life-threatening disseminated BCGitis ranges from 0.06 to 1.56 cases per 1 million individuals worldwide. Saudi Arabia is a country with moderate TB burden, and the annual incidence rate of TB ranges from 14 to 17 cases per 100,000 individuals [4–6].

There are no well-established guidelines for the treatment of disseminated BCGitis in children. However, it is recommended to start aggressive treatment with at least 4 antimycobacterial antibiotics considering the susceptibility pattern [7,8].

Moxifloxacin is a fourth-generation fluoroquinolone and considered as a second-line anti-TB agent in adult patients. It targets DNA gyrase and disrupts DNA synthesis, which leads to cell death. This agent has more than 90% bioavailability and low minimum bactericidal concentration (MBC). In children, there are few clinical data about dosing, safety, and tolerability of moxifloxacin in patients with multidrug-resistant (MDR) TB. The limitation of using quinolone in children is that there is the possibility of musculoskeletal adverse effects [9].

A retrospective study of the management of pulmonary TB in children by using moxifloxacin showed favorable response [10]. In another pharmacokinetic study, moxifloxacin serum concentration in children treated for MDR TB was found to be low with an oral dose of 10 mg/kg, and hence, a higher moxifloxacin dose may be required [11]. On the other hand, there are no clinical data about the use of moxifloxacin in patients with disseminated *M. bovis* BCGitis. This retrospective study aims to report our experience at King Faisal specialist hospital about the dosing, safety, and tolerability of moxifloxacin in children with disseminated BCGitis.

2. Material and method

In this retrospective descriptive study, we included ten children who was diagnosed with disseminated BCGitis and treated with an antimycobacterial regimen including moxifloxacin, for more than two weeks from 2007 to 2017 at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. Moxifloxacin was administered orally at 10 mg/kg/day, and when necessary, the dose increased to 20 mg/kg/day. Patients' tolerance to the drug was reviewed by liver function tests (ALT, AST, ALP, and bilirubin), musculoskeletal adverse effects, or any reported side effect from the patient or their parents. Diagnosis of disseminated BCGitis was based on BCG infection involving any site of the body beyond the vaccination site and ipsilateral lymph node. Surgical samples were observed under a microscope for acid-fast bacilli (AFB) identification; then, the samples were inoculated in BACTEC MGIT TB liquid culture tubes (BD Biosciences, Sparks, MD) and incubated in the BACTEC-MGIT 960 instrument (BD Biosciences) until there was positive detection by the machine. The isolate was confirmed to be *Mycobacterium tuberculosis* by PCR using the GeneXpert MTB/RIF. Sensitivity testing to isoniazid, rifampin, and ethambutol was performed on a BACTEC-MGIT 960 instrument (BD Biosciences)

according to the manufacturer's instructions. Sensitivity to a second-line antimycobacterial agent and moxifloxacin level were determined at Mayo Clinic Medical Laboratories; blood samples were collected approximately 2 h post oral dose, and the therapeutic peak concentration was observed in the range of 3–5 mcg/ml. Patient outcome was classified as improved, the same condition, or death. Improvement was evaluated on the basis of clinical improvement, decrease in the size of lymph nodes, or radiological improvement in children treated with a moxifloxacin-containing regimen for disseminated BCGitis. Data were collected on gender, age, underlying cause of disseminated BCGitis, age at diagnosis of disseminated BCGitis, site of dissemination, source of specimen from which *M. bovis* was isolated, susceptibility testing, antimycobacterial medications while the patient was on moxifloxacin, moxifloxacin duration, reason for adding moxifloxacin, reported adverse effects, and liver function test.

King Faisal Specialist Hospital and Research Center Institutional Review Board approved the retrospective review of the children's clinical records for the purpose of this study.

3. Results

Ten children who were diagnosed with disseminated BCGitis were included in this retrospective descriptive study. Of the 10 children, 6 (60.0%) were male and 4 (40.0%) were female. The mean age of the children was 3.3 years (SD 1.4). The mean age at disseminated BCGitis diagnosis was 7.4 months (SD 2.8). Nine patients had a weight less than the third percentile in the CDC growth chart for sex and age (See Table 1).

The primary diagnosis for five patients was MSMD, four patients were diagnosed with SCID, and the remaining one patient had a HIV infection. The most common site for dissemination was the lymph node (90%), while six patients had dissemination of the skin and lungs. Other sites of dissemination were the bone, spleen, liver, and nasal mucosa (Fig. 1). Surgical resection of the lymph node was performed in 8 patients (80%), and the diagnosis was made on the basis of microscopic tests for AFB, *M. bovis* culture, and mycobacterium tuberculosis PCR (MTB PCR); all patients had been tested positive except for one patient (HIV) who had a negative result for *M. bovis* culture, although his sample showed a positive result for microscopic tests for AFB and for MTB PCR.

Overall mean duration of moxifloxacin treatment was 10.1 months (SD 2.5). The most common reason for adding moxifloxacin was clinical failure while the patient was on ciprofloxacin in 8 out of 10 children (80%) and due to a low level of ciprofloxacin in 2 of 10 (20%) patients. In addition to moxifloxacin, all patients received a regimen that included at least three other antimycobacterial agents that were likely to be sensitive against *M. bovis*. The other antimycobacterial agents concomitantly used with moxifloxacin were ethambutol (100%), clarithromycin (70%), cycloserine (80%), isoniazid (30%), amikacin (30%), and rifampicin (10%). Moxifloxacin serum concentration was determined in 5 patients. The serum level was determined 2 h post oral dose. Liver function test for all patients was performed while they were on moxifloxacin; the test included assessment of liver enzymes, ALT, AST, ALP, and bilirubin, and results show that 6 patients had normal ALT, AST, ALP, and bilirubin, whereas patient number 5 had normal bilirubin but had elevated ALT, AST, and ALP. Patient numbers 8 and 10 had elevated liver enzymes, whereas patient number 9 had elevated bilirubin but normal ALT, AST, and ALP. All patients tolerated moxifloxacin, and no musculoskeletal side effects were reported while the patient was on moxifloxacin. The outcome of the patients showed that six patients had the same condition, two patients died, and patient numbers 4 and 7 had improved (Fig. 2). Primary diagnosis of the deceased patients revealed SCID.

Table 1
Descriptive Analysis for Sociodemographic, Clinical, and Microbiological Characteristics of patients (n = 10).

| Pt No. | Age (years) | Sex | Underlying Cause of Disseminated BCGitis | Time of Disseminated BCGitis Diagnosis | Medication Resistant | Other Antimycobacterial Antibiotics | MXF Duration | MXF Level | MXF Dose | MXF Frequency | Outcome |
|--------|-------------|-----|--|--|----------------------|-------------------------------------|--------------|-----------|----------|---------------|--------------------|
| 1 | 4 | M | SCID | 10 months | INH, RIF, ETO | EMB, AMK, CYC | 9 Months | 0.36 | 10 | QD | Death |
| 2 | 6 | M | MSMD + IL12-RD | 12 months | None | EMB, CLA, CYC | 7 Months | Not taken | 23.9 | QD | The Same Condition |
| 3 | 3 | M | SCID | 4 months | RIF | EMB, AMK, CYC | 23 Months | 5.01 | 11.2 | QD | The Same Condition |
| 4 | 3 | F | MSMD + IL12-RD | 6 months | INH | INH, EMB, CLA | 6.5 Months | Not taken | 10 | QD | Improved |
| 5 | 3 | M | SCID | 10 months | None | INH, EMB, CLA | 1 Month | 4.23 | 20 | QD | The Same condition |
| 6 | 1.17 | M | SCID | 6 months | None | EMB, CLA, CYC | 2 Months | Not taken | 10 | QD | Death |
| 7 | 3 | F | HIV | 6 months | None | EMB, CLA, CYC | 15.5 Months | 2.68 | 10 | BID | Improved |
| 8 | 3 | F | MSMD + IGD | 6 months | INH, ETO | RIF, EMB, CLA, CYC | 8 Months | 1.18 | 12.2 | QD | The Same Condition |
| 9 | 2 | M | MSMD + IL12-RD | 10 months | None | INH, EMB, AMK, CYC | 8.5 Months | Not taken | 20 | QD | The Same Condition |
| 10 | 5 | F | MSMD + IL12-RD | 4 months | INH, RIF, ETO | No data | 21 Months | Not taken | 10 | QD | The Same Condition |

M-Male; F-Female; BCG-Bacille Calmette-Guerin; SCID-Severe Combined Immunodeficiency; MSMD-Mendelian Susceptibility to Mycobacterium Dissemination; IGD-Interferon Gamma Deficiency; IL12-RD-Interleukin 12 Receptor Deficiency; HIV-Human Immunodeficiency Virus; Ethambutol; CLA-Clarithromycin; AMK-Amikacin; ETO-Ethionamide; RIF-Rifampicin; INH-Isoniazid; CYC-Cycloserin; MXF-Moxifloxacin; QD-Once daily; BID-Twice daily. ©MXF Dose-mg/kg.

Site of Dessimination

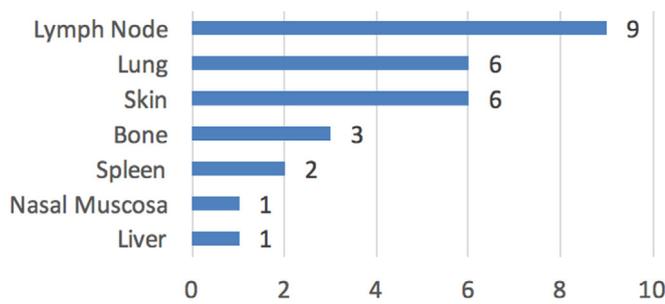


Fig. 1. Distribution of the site of dissemination.

Outcome

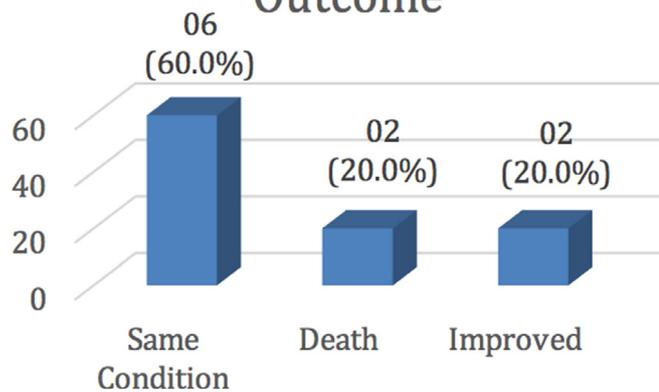


Fig. 2. Distribution of treatment outcome.

4. Discussion

To our knowledge, this is the first study describing pediatric patients with disseminated BCGitis who were treated with moxifloxacin. The objective of our study is to investigate the dosing,

safety, and tolerability of using moxifloxacin in children with disseminated BCGitis.

In our study, moxifloxacin was introduced as an addition to or substitution for other antimycobacterial agents (especially ciprofloxacin) in the treatment of disseminated BCGitis owing to various reasons such as clinical failure, low level of ciprofloxacin, or unavailability of ciprofloxacin. All the patients showed tolerance to moxifloxacin without documented complain. Liver toxicity was recorded in three patients, although it could not be certainly attributed to moxifloxacin, as other hepatotoxic drugs were used at the same time. The most common medications used with moxifloxacin were ethambutol and clarithromycin. The drug level was determined in 5 out of 10 (50%) cases, and among them, 2 cases were therapeutic (3–5 mcg/ml) and were associated with higher doses > 10 mg/kg, but the other 3 cases were associated with a dose of 10 mg/kg. Doses were adjusted according to the reported moxifloxacin level, and the determination of levels was repeated. This result supports the result of the prospective pharmacokinetic and safety South African study, which suggests that 10 mg/kg/day as part of MDR TB treatment is not sufficient and hence suggests a higher dose to be given. In another in vitro study (Goldilocks), the moxifloxacin dose was 20 mg/kg/day for toddlers and school-aged children and 25 mg/kg/day for infants [11,12]. On the basis of a combination of those two studies, we used a dose of more than 10 mg/kg/day and used pharmacokinetics level, clinical response, and adverse events as a guide for optimal doses. One HIV-infected child had low serum moxifloxacin concentration, which might be due to HIV infection itself and its effect on the gastrointestinal tract and absorption or drug–drug interaction [13]. Low serum moxifloxacin concentration was determined in another patient on rifampicin. Serum concentration of moxifloxacin is significantly reduced when moxifloxacin is used with rifampicin because of the potential interaction that could decrease moxifloxacin drug concentrations by up to 31% [14]. Treated patients showed a different response to an antimycobacterial regimen including moxifloxacin with mortality in 2 patients.

The majority of the patients involved in this study were suffering from primary immunodeficiency. The primary immunodeficiency incidence is quite high in Saudi Arabia because of consanguinity. Disseminated mycobacterial diseases secondary to

M. bovis-containing vaccine (BCG) are frequently seen in a patient with primary immunodeficiency such as MSMD, SCID. Such primary immunodeficiency could jeopardize the patient to develop a severe and invasive infection by some microorganism such as *M. bovis* (BCG), *M. tuberculosis*, and *Salmonella*. Prompt start of an antimycobacterial agent with at least four medications is recommended if the patient has disseminated BCGitis, although there are no clear guidelines on the most suitable treatment for disseminated BCG disease [15,16].

In a retrospective in vitro study, a high susceptibility rate of moxifloxacin to *M. bovis* was observed, with minimum inhibitory concentration (MIC) in the range of 0.06–0.25 µg/ml. Moreover, moxifloxacin has excellent bioavailability of up to 90% and wide tissue diffusion with bactericidal activity [17]. Moxifloxacin has superior antimycobacterial activity compared to other fluoroquinolones; it has bactericidal activity, and it is a concentration-dependent antibiotic with a favorable pharmacodynamics profile in addition to levofloxacin [9,18,19].

Fluoroquinolones are highly important therapeutic agents usually required for MDR TB and disseminated BCGitis. The possibility of arthropathy in animal studies makes fluoroquinolone use in children limited. Some of the studies in children reported arthralgia/arthritis with the use of fluoroquinolones (MXF), which necessitates the stop of treatment. Prolongation of QT interval is a known side effect for moxifloxacin, and unfortunately, there were no baseline ECG data of our patients in the study before and after starting moxifloxacin [20,21].

Garazzino et al. described nine pediatric patients treated with a moxifloxacin (10 mg/kg)-containing regimen for pulmonary TB. The mean moxifloxacin duration was 6.8 months. One case of arthritis and another case with possible hepatotoxicity secondary to moxifloxacin have been reported. All the children involved in their study showed radiological and clinical cure [10]. Pinon M et al. reported two cases of MDR TB that have been treated with a moxifloxacin-containing regimen, and both cases showed improvement without side effects [22].

In this study, we have a limitation in the timing of the moxifloxacin level in some cases. In addition to the small number of cases, the study was retrospective rather than prospective.

In conclusion, our study suggests that moxifloxacin is generally tolerated in children and might be considered in disseminated BCGitis cases. Additionally, paying attention to side effects such as liver toxicity is recommended particularly with other antimycobacterial agents, which could also be hepatotoxic. The moxifloxacin-containing regimen for disseminated BCGitis has showed clinical improvement in some patients in this study, although the majority of them have presented the same clinical condition. A further prospective study is recommended to assess side effects, serum level, and long-term safety of moxifloxacin in pediatrics with TB or disseminated BCGitis.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical statement

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. The publication of this report was approved by the Ethics Review Board of King Faisal Specialist Hospital and Research Centre (KFSHRC). We have read and understood the journal's policies and believe that neither the manuscript nor the study violates any of these policies. There are no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpam.2019.01.003>.

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