

# LINEZOLID IN THE TREATMENT OF DISSEMINATED NONTUBERCULOUS MYCOBACTERIAL INFECTION IN ANTI-INTERFERON- $\gamma$ AUTOANTIBODY-POSITIVE PATIENTS

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**Abstract.** Disseminated nontuberculous mycobacterial (NTM) infection is the most common feature in patients positive for anti-interferon-gamma autoantibody (IFN- $\gamma$  Ab). The condition is a form of anticytokine autoantibody syndrome. It is difficult to treat because of multiple drug resistance in mycobacteria. Linezolid is active against NTM *in vitro*; however clinical experience using this drug against NTM is limited. We report our experience using linezolid as part of an antimycobacterial regimen for treatment of 16 refractory cases of disseminated NTM at Srinagarind University Hospital, Khon Kaen, between September 2008 and December 2012. Complete resolution of signs and symptoms was seen in eight patients (50%) on linezolid therapy. Partial or no improvement was seen in a further four (25%) and three (19%) cases, respectively. Five (31%) patients developed an adverse reaction to linezolid; three of whom received 600 mg of linezolid twice daily. The study demonstrated the modest efficacy of linezolid for treating patients with a protracted course of disseminated-NTM; however, adverse effects were significant, especially for those on the high-dosage regimen.

**Keywords:** disseminated nontuberculous mycobacterial infection, linezolid, treatment, IFN- $\gamma$  antibody

## INTRODUCTION

The previously unrecognized clinical entity of disseminated nontuberculous mycobacterial (NTM) infection in non-HIV infected patients has been reported in Thailand since 2000 (Chetchotisakd *et al*, 2000). It is characterized by chronic generalized lymphadenitis with other opportunistic co-infections and reactive

skin diseases (Chetchotisakd *et al*, 2000; 2007). Subsequent study demonstrated that most of the patients tested positive for anti-interferon-gamma autoantibodies (IFN- $\gamma$  Ab), resulting in adult-onset immunodeficiency (Browne *et al*, 2012b). These patients were difficult to treat as they required prolonged courses of combinations of oral antimicrobial therapy. Some patients had persistent infections with repeated positive cultures despite such treatment.

Treatment of infections due to NTM remains difficult, in part because they are resistant to many anti-tuberculous drugs

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and also because few other antimicrobial agents are available for treatment. Linezolid—an oxazolidinone—is approved for treatment of gram-positive bacterial infections. Its mechanism of action is inhibition of protein synthesis at an early stage of the life cycle (Leach *et al*, 2011). Although linezolid has shown good activity against many strains of NTM—both rapidly growing mycobacteria (RGM) and slowly growing mycobacteria (SGM) (Cavusoglu *et al*, 2007; Brown-Elliott *et al*, 2003)—we found only a few case reports on treatment of NTM using linezolid (Brown-Elliott *et al*, 2001; Nannini *et al*, 2002; Morales *et al*, 2007; Furuya *et al*, 2008). Essentially, clinical experience with linezolid for treatment of disseminated-NTM has been limited by small sample sizes. Herein, we report a large case series, which may clarify the role of linezolid in treating disseminated-NTM.

#### MATERIALS AND METHODS

This was a retrospective study at Srinagarind University Hospital, in Khon Kaen, northeastern Thailand, between 1 September 2008 and 31 December 2012. All disseminated NTM cases who received linezolid as part of their antimycobacterial regimen were recruited. Data were censored on 31 December 2012. The medical records of all study patients were reviewed; information on patient demographic characteristics, underlying diseases, clinical details of organ involvement, radiographic and microbiological results, treatment regimens, durations, clinical outcomes, and regimen toxicities and tolerability were recorded. The safety and tolerability of linezolid were determined by reviewing, monthly to bi-monthly, complete blood counts, alanine aminotransferase (ALT) levels, aspartate

aminotransferase (AST) levels, and inquiries regarding neuropathy.

The treatment outcome of linezolid-containing regimens was assessed in two phases: outcomes during linezolid treatment and after its discontinuation. Treatment outcomes (at the end of treatment or during treatment) were: (a) a complete response—complete resolution of clinical signs and symptoms; (b) a partial response—incomplete resolution of clinical signs and symptoms; and, (c) not improved—no clinical improvement or worsened clinical status. After discontinuation, outcomes were: (a) a complete response—complete resolution of clinical signs and symptoms; (b) relapsed—initial response but recurrence of clinical signs and symptoms or a positive culture for NTM; or (c) persistent—no clinical improvement or partial improvement with need of continued antimicrobial treatment.

Diagnosis of NTM infection among these patients was confirmed by isolation of the pathogens from sterile site clinical specimens (*ie*, lymph node, blood, ascites) and classified as RGM and SGM. Since our laboratory does not perform species identification, some of the isolates were sent to the Microbiology Laboratory at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA.

All but one of the patients were enrolled in the adult onset immunodeficiency syndrome study and tested positive for IFN- $\gamma$  Ab (Browne *et al*, 2012b).

Linezolid was administered orally at a dose of 600 mg twice daily in the first five cases. In light of the evolving data that lower doses were still effective in mycobacteria, the dosage of linezolid was

decreased to 600 mg daily and continued at that level throughout the treatment. The study protocol was reviewed and approved by the Institutional Review Board of Khon Kaen University (HE561015).

## RESULTS

There were 16 cases of disseminated-NTM who received linezolid as part of their salvage treatment regimens during the study period (Table 1). All of the patients had multiple lymphadenitis and 75% (12/16) had other organ involvement. Most (15/16; 93.8%) had some type of reactive skin disease (*viz*, Sweet's syndrome, acute generalized erythematous pustulosis, erythema nodosum or leukocytoclastic vasculitis). Most of the patients (14/16) had co-infections with other intracellular pathogens. These co-infections (whether antecedent or concurrent) were successfully treated with specific antimicrobial therapies. Four cases had more than one NTM infection. *Mycobacterium abscessus* was the most common pathogen. Fifteen cases were tested for IFN- $\gamma$  Ab and all of them tested positive. We also included case No.1—who was not tested for IFN- $\gamma$  Ab—but she had a similar clinical entity of adult onset immunodeficiency condition and presented with disseminated NTM with Sweet's syndrome (Chetchotisakd *et al*, 2007).

Patients received multiple regimens of antimicrobial treatment for NTM with the median (range) number of previous regimens being 3.5 (1-8) and the median (range) duration of previous treatment being 24.5 (4-121) months. Five (31%) patients developed adverse reactions to the linezolid. Among these, three were in-patients who received a high dosage of linezolid (*viz*, 600 mg/twice a day). Two of these cases had anemia (one with

thrombocytopenia); one developed rash and one refused to continue the linezolid. Of the two other cases who were started on 600 mg linezolid /day, one had nausea, vomiting and myalgia until the dosage was reduced to 300 mg/day, while the other had numbness of the tongue. In the latter case, linezolid was discontinued because of a lack of any clinical response. The median (range) duration of linezolid treatment was 6 (0.25-44.5) months.

The respective clinical outcome during or at the end of linezolid therapy for a complete response, a partial response and not improved was 8 (50%), 4 (25%) and 3 (19%) cases. One patient died one week after taking medication, the cause of death was unknown. On the date for data censoring, one additional patient (#9) died from a fungal brain abscess. Only three patients continued taking linezolid. The outcomes of the 14 surviving patients were: 4 relapsed, 5 persistent and 5 complete response.

## DISCUSSION

The clinical manifestations in these patients were similar to those in our previous reports (Chetchotisakd *et al*, 2000; 2007): NTM lymphadenitis with other intracellular co-infections and reactive skin diseases. These manifestations reflect immunodeficiency due to IFN- $\gamma$  Ab (Browne *et al*, 2012b). This clinical syndrome is prevalent in Asian populations with genetic associations (Chetchotisakd *et al*, 2000; 2007; Browne *et al*, 2012b; Tanaka *et al*, 2007; Koya *et al*, 2009; Chi *et al*, 2013; Wongkulab *et al*, 2013). Our patients had prolonged courses of NTM infection with the median duration of previous treatment being 24.5 months. Most of the pathogens were resistant to several oral antimicrobial agents, resulting in intermit-

Table 1  
 Summary of demographics and clinical outcomes of 16 patients with protracted course of disseminated nontuberculous mycobacterial infection and who were positive for anti-interferon-gamma autoantibody.

| Case | Sex; Age (year) | IFN- $\gamma$ antibody | Organ involvement                                | Reactive skin disease  | Co-infection                  | NTM pathogen                      | Sequence of NTM treatment regimens before adding linezolid (Duration (month), regimens)                           | Total duration of NTM treatment before adding linezolid (month) | Sequence of NTM regimen during linezolid add-on therapy | Dose (mg/day); Adverse events | Outcome at the end of linezolid treatment |                   |
|------|-----------------|------------------------|--|------------------------|-------------------------------|-----------------------------------|---|---|---|-------------------------------|---|-------------------|
| 1    | F; 53           | Not done               | LN, liver, spleen, blood, lung, skin             | Sweet's syndrome       | None                          | Slow grower                       | R1: 2HRE<br>R2: 4.5HR<br>R3: 15HRECO<br>R4: 1HRECOA<br>R5: 15.5HRECO  | 38  | HREOZ   | 1,200; 1 week                 | None                                      | Death             |
| 2    | F; 47           | +ve                    | LN, bone   | Sweet's syndrome       | Cryptococcosis                | <i>M. abscessus</i>               | R1: 2ECF<br>R2: 2CF   | 4   | CP  | 600; 4.5                      | None                                      | Complete response |
| 3    | M; 61           | +ve                    | LN   | Sweet's syndrome       | None                          | <i>M. abscessus</i>               | R1: 2CAF<br>R2: 27.5CF  | 29.5  | CO  | 600; 6                        | None                                      | Complete response |
| 4    | F; 15           | +ve                    | LN, skin   | Sweet's syndrome, AGEF | Herpes zoster                 | Slow grower, <i>M. fortuitum</i>  | R1: 6HRECO<br>R2: 9HECO<br>R3: 1HREOZA<br>R4: 5HREOZ+2P<br>R5: 2REOZ+0.5P   | 23  | REOZ  | 600; 8                        | None                                      | Complete response |
| 5    | F; 47           | +ve                    | LN, lung   | Sweet's syndrome       | None                          | <i>M. preteregrinum</i>           | R1: 7COE<br>R2: 12HREOZ   | 19  | R1: 2HREOZ<br>R2: 3.5ROZ                                | 600; 5.5                      | None                                      | Partial response  |
| 6    | M; 48           | +ve                    | LN, liver, skin, lacrimal gland, chylous ascites | AGEF                   | Herpes zoster                 | Slow grower, <i>M. abscessus</i>  | R1: 1COPA<br>R2: 5CO+1P<br>R3: 3HREOZA+0.5P<br>R4: 9HREOZ+2P  | 18  | HREOZ+1P  | (1200; 1), (600; 6)           | None                                      | Not improved      |
| 7    | F; 45           | +ve                    | LN, bone, skin                                   | Sweet's syndrome       | Herpes zoster                 | <i>M. abscessus</i>               | R1: 6CA+1P<br>R2: 33C<br>R3: 21CD<br>R4: 2CDOA<br>R5: 59CO+0.5P   | 121   | CO  | 600; 5                        | None                                      | Complete response |
| 8    | F; 43           | +ve                    | LN, liver, blood                                 | Sweet's syndrome       | Cryptococcosis, herpes zoster | <i>M. abscessus</i> , slow grower | R1: 8CO<br>R2: 1ECO<br>R3: 2CO<br>R4: 1COA<br>R5: 7.5CO+1I<br>R6: 6.5HECO<br>R7: 2.5HECOA+1P<br>R8: 24.5HECO+0.5P | 53  | HEOC  | 600; 6                        | None                                      | Complete response |

Table 1 (Continued).

| Case | Sex; Age (year) | IFN- $\gamma$ antibody | Organ involvement                 | Reactive skin disease                          | Co-infection  | NTM pathogen   | Sequence of NTM treatment regimens before adding linezolid (Duration (month), regimens)                | Total duration of NTM treatment before adding linezolid (month) | Sequence of NTM treatment regimens during linezolid add-on therapy          | Dose (mg/day); duration of linezolid treatment (month) | Adverse events                    | Outcome at the end of linezolid treatment | Current outcome   |
|------|-----------------|------------------------|-----------------------------------|--|---|--|--|---|---|--|-----------------------------------|---|-------------------|
| 9    | F; 42           | +ve                    | LN, liver, spleen, lacrimal gland | EN, suppurative folliculitis, Sweet's syndrome | Salmonellosis, tuberculosis, herpes zoster, Cladophiala-phora brain abscess | Rapid grower<br><i>M. abscessus</i> ,<br><i>M. fortuitum</i>       | R1: 5OZ+1.5P<br>R2: 6CO+1P<br>R3: 13CM+3.5P  | 24  | R1: 6CM+3P<br>R2: 7.5CO+3P<br>R3: 0.5A<br>R4: 1CA<br>R5: 2A+0.5P<br>R6: 8CO | (1,200; 3), (600; 22)                                  | Anemia                            | Partial response                          | Death             |
| 10   | F; 47           | +ve                    | LN, sinus, skin, tonsil           | None   | Herpes zoster   | <i>M. simiae</i> ,<br><i>M. abscessus</i> ,<br><i>M. fortuitum</i> | R1: 15COA<br>R2: 2COAE<br>R3: 9C<br>R4: 5COAE<br>R5: 4HRCOAE<br>R6: 17HRCOE<br>R7: 3HEOF<br>R8: 5HECOA | 60  | R1: 1HECOP<br>R2: 40.5HECO<br>R3: 3 HCO                                     | (1,200; 3), (600; 41.5)                                | Anemia, Thrombocytopenia          | Complete response                         | Complete response |
| 11   | F; 45           | +ve                    | LN                                | AGEP   | Chickenpox  | <i>M. fortuitum</i>  | R1: 20.5ECO  | 20.5  | EOC   | 600; 3.5   | Numbness of tongue                | Not improved                              | Persistent        |
| 12   | F; 57           | +ve                    | LN, liver, spleen, blood          | Pustular psoriasis                             | Salmonellosis, herpes zoster  | <i>M. abscessus</i>  | R1: 1CAP<br>R2: 5CA<br>R3: 12C<br>R4: 14CD<br>R5: 43.5CO   | 75.5  | CO  | 1,200, 5 days  | Rash<br>Premature discontinuation | Not improved                              | Persistent        |
| 13   | F; 48           | +ve                    | LN, spine, paravertebral abscess  | Sweet's syndrome                               | Cryptococcosis  | <i>M. abscessus</i>  | R1: 32COE+1P<br>R2: 37CO+2X+2A+1P  | 69  | R1: 7CO+1P  | (600; 0.5), (300; 6.5), continuing                     | Nausea, vomiting, myalgia         | Partial response                          | Persistent        |
| 14   | M; 63           | +ve                    | LN, bone, liver                   | AGEP, LCV                                      | Histoplasmosis, herpes zoster   | <i>M. abscessus</i>  | R1: 14.5CO+1P  | 14.5  | R1: 4CO+0.5P  | 600; 4, continuing                                     | None                              | Complete response                         | Complete response |
| 15   | M; 34           | +ve                    | LN                                | Sweet's syndrome                               | Cryptococcosis, tuberculosis  | <i>M. abscessus</i>  | R1: 3.5+0.5P<br>R2: 12ZO+5P  | 15.5  | R1: 18CO+0.5P   | 600; 18, continuing                                    | None                              | Partial response                          | Persistent        |
| 16   | F; 34           | +ve                    | LN                                | AGEP<br>EN                                     | Herpes zoster   | <i>M. abscessus</i>  | R1: 3.5HCOE<br>R2: 1.5CO<br>R3: 2COA+1P<br>R4: 2CO+1P  | 9   | CO  | 600mg; 12.5  | None                              | Complete response                         | Complete response |

NTM, nontuberculous mycobacterial; F, female; M, male; LN, lymph node; R, regimen; AGEF, acute generalized erythematous pustulosis; EN, erythema nodosum; LCV, leukocytoclastic vasculitis, H: isoniazid; R, rifampicin; E, ethambutol; O, ofloxacin; F, ciprofloxacin; M, moxifloxacin; C, clarithromycin; Z, azithromycin; D, doxycycline; A, amikacin; P, imipenem; X, cefoxitin.

tent hospitalization for rescue administration of imipenem or ceftazidime.

There were significant adverse effects (31%) related to linezolid in these patients, especially for those taking a high dose (1,200 mg of linezolid/day) as also reported when linezolid was used for treatment of extensive drug-resistant tuberculosis (XDR-TB) (Anger *et al*, 2010). Low-dose linezolid (300 mg/day) has been studied in XDR-TB with promising results (Lee *et al*, 2012). The outcomes at the end of linezolid treatment in our patients were modest: 12 cases (75%) had complete or partial responses to the regimen but most experienced a persistent or relapsed infection. The reasons for the poor outcomes might be the short duration of treatment or development of resistance to the linezolid. We could not determine any correlation between the quantity of IFN- $\gamma$  Ab and active NTM disease or response to linezolid treatment since only one random serum sample was tested for IFN- $\gamma$  Ab in each patient during the course of the NTM infection. But we consider that the most likely culprit—based on the associated evidence—is the presence of IFN- $\gamma$  Ab. In a recent study, use of rituximab, anti-CD20, was reported as an adjunctive immunotherapy for treating four cases of adult-onset acquired immunodeficiency syndrome with refractory disseminated nontuberculous mycobacteria and the presence of high-titer IFN- $\gamma$  Ab (Browne *et al*, 2012a). This is promising evidence of a clinical response, which correlates with autoantibody titer reduction and amelioration of plasma-mediated IFN- $\gamma$  signaling inhibition. This evidence supports the role of adjunctive immunotherapy for control of underlying acquired immunodeficiency and improving the clinical outcome of NTM infections.

In conclusion, linezolid is useful

for the treatment of disseminated-NTM infection, particularly in those with limited choices for oral therapy. Low-dose linezolid can be safe and effective. The efficacy of combinations of antimicrobial treatment with other adjunctive therapies for diminishing autoantibodies in patients with IFN- $\gamma$  Ab with NTM infection—especially refractory cases—should be further investigated.

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