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Combined administration of rifampicin, ethambutol, and clarithromycin for the treatment of tenosynovitis of the hand caused by *Mycobacterium avium* complex

Case series and literature review

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Abstract

We report the clinical results and problems of combined administration of rifampicin, ethambutol, and clarithromycin (REC) for the treatment of *Mycobacterium avium* complex (MAC) infection of the hand (hand MAC).

Participants included 7 patients with hand MAC. After resection of the infected lesion, REC was prescribed for 12 months. For these patients, the site of infection, clinical course after initiation of REC, adverse drug effects (ADEs), and incidence of recurrence were evaluated.

Sites of infection were the flexor tenosynovium in 5 patients, extensor tenosynovium in 1 patient, and both flexor and extensor tenosynovium in 1 patient. ADEs of REC occurred in 5 patients, and included visual disturbance caused by ethambutol in 2 patients, liver function abnormality caused by rifampicin in 2 patients, and fever with diarrhea caused by rifampicin in 1 patient. For 2 of these 5 patients, desensitization therapy was applied and REC was able to be reinstated. In the remaining 3 patients, the causative drugs were discontinued and levofloxacin, a new quinolone, was administered. Complete healing was achieved in 5 patients, and recurrence was observed in 2 patients. These 2 patients with recurrence included 1 patient in whom REC was completed and 1 patient in whom REC therapy was modified due to ADE.

REC provided relatively good clinical results as a treatment for hand MAC. However, recurrences were observed even after the completion of REC and the use of an alternative drug. Optimal duration of REC and appropriate alternative drugs need to be identified in the future.

Abbreviations: ADEs = adverse drug effects, ATS/IDSA = The American Thoracic Society and the Infectious Diseases Society of America, BTS = The British Thoracic Society, CAM = clarithromycin, EB = ethambutol, hand MAC = MAC infection of the hand, LVFX = levofloxacin, MAC = *Mycobacterium avium* complex, NTM = nontuberculous mycobacteria, PCR = polymerase chain reaction, pulmonary MAC = pulmonary MAC infection, RA = rheumatoid arthritis, REC = combined administration of rifampicin, ethambutol, and clarithromycin, RFP = rifampicin, SLE = systemic lupus erythematosus.

Keywords: clarithromycin, ethambutol, *Mycobacterium avium* complex, rifampicin, tenosynovitis

1. Introduction

Although nontuberculous mycobacteria (NTM) are widely distributed in the water and soil,[1] human infection with NTM is uncommon. Among NTM infections, pulmonary disease is the most common clinical presentation. In particular, *Mycobacterium avium* complex (MAC) is the most common cause of pulmonary NTM infection.[2] On the other hand, NTM infection of the hand is a very rare condition compared with pulmonary NTM infection. Among cases of NTM infection of the hand, *M marinum* is known to be the most common cause,[3] but MAC is also known to cause NTM infection in the hand.[4–8]

Regarding chemotherapy for MAC infection, several therapeutic guidelines and recommendations have been made for pulmonary MAC infection (pulmonary MAC).[9–11] Among these, combined administration of rifampicin (RFP), ethambutol (EB), and clarithromycin (CAM) (REC) is the most popular therapeutic regimen. For MAC infection of the hand (hand MAC), many therapeutic regimens have been tried, including several antituberculous drugs, macrolides, and new quinolones.[12] Among reports of hand MAC, several reports have described the use of REC.[1,4,5] However, as almost all of those

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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reports have been single case reports or small case series, the efficacy of REC for hand MAC remains unclear.

Our institution has routinely used REC for hand MAC since 2009. The aim of this study was to report the clinical results and problems of REC for hand MAC.

2. Methods

This study was approved by the ethics committee at our institution (Heisei27-120), and informed consent for publication of this article was obtained from the patients.

2.1. Study patients

This retrospective study included 7 patients (4 men, 3 women; mean age, 67.4 years; range, 58–78 years) with chronic flexor or extensor tenosynovitis in the hand (Table 1). The diagnosis of hand MAC was confirmed by polymerase chain reaction (PCR) or mycobacterial culture of a sample of tenosynovium collected by open biopsy or tenosynovectomy.

2.2. PCR examination and mycobacterial culture

For PCR examination of collected synovial tissue, real-time PCR assay was performed using MAC detection kit (Cobas TaqMan MAI; Roche Diagnostics, Basel, Switzerland). Mycobacterial culture was performed on Ogawa medium (Ogawa K Medium; Kyokuto Pharmaceutical, Tokyo, Japan). MAC was identified from colonies formed on the medium using real-time PCR.

2.3. Treatment

All patients underwent massive tenosynovectomy of the involved tendon. REC was initiated postoperatively. The therapeutic doses of RFP, EB, and CAM were decided in accordance with the Japanese guideline for pulmonary MAC from the Japanese Society for Tuberculosis and Nontuberculous Mycobacteriosis.[11] Basic dosages of the 3 drugs were 10, 15, and 15 mg/kg/d, respectively, adjusted according to age, renal function, and liver function of each patient. When adverse drug effects (ADEs) of these drugs were observed, administration of the causative drug was discontinued. After discontinuation of the causative drug, levofloxacin, a new quinolone, was administered as an alternative. If the ADEs were caused by RFP and consensus was obtained from the patient, hyposensitization therapy was tried. If hyposensitization therapy succeeded, REC therapy was reinitiated for the patient. REC was basically continued for 12 months.

2.4. Outcome assessment

The following data were collected from the medical records of patients: duration from the onset of disease to diagnosis, sites of infection, past histories including autoimmune disease, diabetes, use of immunosuppressants (such as corticosteroid and methotrexate), results of diagnostic testing (including pathological evaluation, PCR examination, and mycobacterial culture), therapeutic drugs, ADEs, recurrence, and residual disability.

3. Results

Mean duration from onset of disease to diagnosis was 7.7 months (range, 1–15 months). Past history included rheumatoid arthritis (RA) in 1 case, systemic lupus erythematosus (SLE) in 1 case, asthma in 1 case, and renal dysfunction in 1 case. One patient with RA and 1 patient with SLE had used both corticosteroid and methotrexate. Sites of infection included the flexor tenosynovium in 5 cases, extensor tenosynovium in 1, and both in 1. Pathological evaluations revealed epithelioid granuloma in 6 patients and nonspecific inflammation in 1 patient (Table 1). The results of other diagnostic tests were as follows. MAC was detected by mycobacterial culture in 4 patients and by both mycobacterial culture and PCR examination in 3 patients. MAC was not detected by PCR examination alone in any patients. The strain was *M intracellulare* in 6 of the 7 patients and *M avium* in 1 patient.

Mean dosages of RFP, EB, and CAM were 450 mg/d (range, 400–600 mg/d), 661 mg/d (range, 500–750 mg/d), and 486 mg/d (range, 400–600 mg/d), respectively. ADEs were observed in 5 patients. Visual disturbance caused by EB was observed in 2 patients. For these 2 patients, administration of EB was discontinued and levofloxacin (LVFX), a new quinolone, was prescribed as an alternative. Liver function abnormality in 2 patients and fever and diarrhea in 1 patient were observed as ADEs of RFP. For 1 patient, administration of RFP was discontinued and LVFX was prescribed. For the remaining 2 patients, desensitization therapy was successfully applied. REC was therefore reinitiated. In total, REC was able to be completed in 4 of our 7 patients (Table 2).

Recurrence was observed in 2 patients, one of whom was a male with flexor tenosynovitis in whom the ADE of EB was observed. In that patient, administration of EB was discontinued and LVFX was prescribed in its place. However, the patient developed recurrence at 5 months after initiation of chemotherapy. For this patient, tenosynovectomy was performed again and combined administration of RFP, CAM, and minocycline was prescribed. This chemotherapy was stopped on the request of the patient at 7 months after initiation of second chemotherapy.

Table 1

Patient characteristics.

Case	Age	Sex	History	Use of immunosuppressants	Site of infection	Histological findings
1	58	M			Flexor tendon	Epithelioid granuloma
2	69	M	RA	CS+MTX	Flexor tendon	Epithelioid granuloma
3	66	F			Flexor tendon	Epithelioid granuloma
4	78	F			Flexor tendon	Epithelioid granuloma
5	72	M	Asthma		Extensor tendon	Epithelioid granuloma
6	67	F	SLE	CS+MTX	Flexor and extensor tendon	Epithelioid granuloma
7	63	M	Renal dysfunction		Flexor tendon	Nonspecific inflammation

CS = corticosteroid, MTX = methotrexate, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus.

Table 2

Diagnosis of *Mycobacterium avium* complex and treatment.

Case	Diagnostic testing		Agent	Adverse effects	Medication	Recurrence
	Culture	PCR				
1	+	−	*M avium*	Visual disturbance	REC → RFP, CAM, LVFX	+
2	+	+	*M intracellulare*	Visual disturbance	REC → RFP, CAM, LVFX	−
3	+	−	*M intracellulare*	Liver dysfunction	REC → EB, CAM, LVFX	−
4	+	+	*M intracellulare*	Liver dysfunction	REC (+DT)	+
5	+	−	*M intracellulare*	Liver dysfunction	REC (+DT)	−
6	+	+	*M intracellulare*	−	REC	−
7	+	−	*M intracellulare*	−	REC	−

CAM = clarithromycin, DT = desensitization therapy, EB = ethambutol, LVFX = levofloxacin, REC = combined administration of rifampicin, ethambutol, and clarithromycin, RFP = rifampicin.

However, no recurrence has been observed as of 9 years after the end of treatment. Another patient was a 78-year-old elderly woman with flexor tenosynovitis. For this patient, 12 months of REC was completed, but she developed recurrence at 8 months after completion of therapy. After this recurrence, she again received tenosynovectomy and combined administration of RFP, EB, CAM, and LVFX was prescribed. However, the patient died from influenza 7 months after initiation of second chemotherapy. During the second chemotherapy, no evidence of recurrence was observed in her hand (Table 3).

Complications included finger contracture and flexor tendon rupture. Mild or moderate finger contracture caused by tendon adhesion was observed in all patients. Flexor tendon rupture of the little finger was observed in 1 patient, and was treated with tendon transfer 12 months after the end of REC.

4. Discussion

For the treatment of hand MAC, combinations of several antimycobacterial drugs, CAM, and new quinolones have been used, but no standard drug regimen has been determined.[4,8,13,14]

On the other hand, several standard drug regimens are applied for the management of pulmonary MAC in different countries. The American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) published an official clinical guideline on the diagnosis and treatment of NTM diseases.[9] This guideline recommends combined treatment comprising macrolide (CAM or azithromycin), EB, and RFP for initial therapy of pulmonary MAC. The British Thoracic Society (BTS) also recommended that nonsevere MAC pulmonary disease be treated with RFP, EB, and CAM or azithromycin.[10] Japan likewise has a guideline for the treatment of pulmonary MAC, from the Japanese Society for Tuberculosis and Nontuberculous Mycobacteriosis.[11] This guideline recommends combined treatment with RFP, EB, and CAM. Given these various guidelines, REC may also be effective for the treatment of hand MAC. Indeed, ATS/IDSA recommends using the same drug regimen in pulmonary MAC as for the treatment of extrapulmonary MAC, including tendons. Moreover, several reports have described use of REC for the treatment of hand MAC.[4–6] Most such reports were single case reports and the duration of medication differed between reports. Determining the effectiveness of REC against hand MAC is thus difficult.

Since 2009, we have been routinely prescribing REC for hand MAC and reported our clinical results and the difficulties we encountered in this study. In this study, the biggest problem was the extremely high incidence of ADEs. Miwa et al[15] also observed ADEs of REC in 22 of 59 patients (37.2%) with pulmonary MAC.

Once ADEs arise, we need to either change the causative drug to an alternative drug or try desensitization therapy. ADEs are usually caused by RFP or EB, but rarely by CAM. In this study, ADEs were observed in 5 of 7 patients, caused by RFP in 3 patients and by EB in 2 patients. If the ADEs were due to RFP, desensitization therapy is known to sometimes work well.[16–18] Indeed, we were able to reinitiate REC for 2 of 3 patients in whom the ADEs of RFP were observed. On the other hand, although some reports have described desensitization therapy for ADEs of EB.[16,18] If the ADE is visual disturbance, desensitization therapy is not usually used, because the visual disturbance sometimes becomes irreversible. In this study, as all ADEs caused by EB represented visual disturbance, we gave up on desensitization therapy and prescribed other alternative drugs.

Regarding alternative drugs for RFP or EB, reliable data are lacking regarding the best alternative. Our hospital mainly used LVFX, a new quinolone, as an alternative, because some reports have described the use of new quinolones for the treatment of MAC.[19–21] However, the efficacy of these against MAC infection is still unclear.[22,23] Indeed, we experienced recurrence during the treatment using LVFX as an alternative of EB. Therefore, it is necessary to search for an appropriate alternative for RFP or EB in the future.

Regarding the duration of medication, ATS/IDSA, BTS, and JST recommend 12 months of REC after culture conversion in the treatment of pulmonary MAC. ATS/IDSA also recommend continuing the medication for 6 to 12 months for the treatment of tendon and joint MAC infection. However, they also mention

Table 3

Time courses of patients with recurrence.

Case	Medication after second synovectomy	Duration of second therapy (months)	Result of second therapy
1	RFP, CAM, MINO	7 → Refused medication	Cured
2	REC+LVFX	7 → Death	Died from influenza

CAM = clarithromycin, LVFX = levofloxacin, MINO = minocycline, RFP = rifampicin.

that they do not know whether the duration of treatment for tendon and joint MAC is optimal.[9] In this study, we basically continued REC for 12 months. However, we experienced recurrence in 1 patient after the completion of 12 months of REC. Therefore, 12 months of REC may be inadequate for some types of hand MAC. Saraya et al[5] reported a patient who was treated for hand MAC using 6 months of REC and experienced recurrence. For this patient, they reinitiated REC and continued for 18 months, and they finally succeeded the treatment.[5] This fact also suggests that 12 months of treatment is insufficient for hand MAC and may require a longer duration.

Several reports have mentioned the relationship between treatment failure of musculoskeletal NTM infection and the immune status of patients. Kozin and Bishop[24] reported that in 15 immunocompetent patients with musculoskeletal NTM infection, the disease resolved in 13 patients. However, in 10 immunocompromised patients, resolution was only seen in 4 patients.[24] Park et al[12] also reported failure of treatment for immunocompromised patients with hand MAC. These reports suggest immunocompromised status as a risk factor for treatment failure. On the other hand, although 2 patients experienced treatment failure, both patients were immunocompetent. This fact suggests that several factors other than immune status may affect the outcome of REC for hand MAC.

A key limitation of the present study was that the sample size was small compared with investigations of other popular diseases. However, the reports of 7 cases in which the same drug regimen was prescribed for hand MAC represent a considerably large sample size among reports of hand MAC. We believe that our report will provide helpful information for future treatment of hand MAC.

In conclusion, if patients completed 12 months of REC or modified REC in which drugs causing ADEs were changed to a new quinolone, relatively good therapeutic results were obtained. On the other hand, we encountered cases in which recurrence occurred. To further improve treatment results, the optimal treatment period and appropriate alternative drugs need to be identified.

Author contributions

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