Volume 73, Number 2
*Printed in the U.S.A.*
(ISSN 0148-916X)

# CORRESPONDENCE

*This department is for the publication of informal communications that are of interest because they are informative and stimulating, and for the discussion of controversial matters. The mandate of the JOURNAL is to disseminate information relating to leprosy in particular and also other mycobacterial diseases. Dissident comment or interpretation on published research is of course valid, but personality attacks on individuals would seem unnecessary. Political comments, valid or not, also are unwelcome. They might result in interference with the distribution of the JOURNAL and thus interfere with its prime purpose.*

## The Role of Mycophenolate Mofetil in the Treatment of Leprosy Reactions

TO THE EDITOR:

Leprosy or Hansen's disease (HD) is often complicated by immune-mediated reactions. Reversal reaction (RR), a delayed type hypersensitivity response, can occur in borderline tuberculoid (BT), borderline borderline (BB) and borderline lepromatous (BL) patients. Erythema nodosum leprosum (ENL) is an antibody immune complex reaction that occurs in BL and lepromatous (LL) patients. The standard treatment for RR is systemic corticosteroids, whereas thalidomide is the most effective drug for ENL ([2, 5, 10]). While steroids provide rapid control of ENL symptoms, long term use often results in the associated adverse effects ([11]). Three patients with leprosy reactions and thalidomide or steroid toxicities were treated with mycophenolate mofetil (MMF) as a steroid sparing agent and their outcomes described below.

**Case 1.** A 29-year-old Hispanic male was diagnosed with BL (slit smear average of 4.5) and started on daily rifampin 600 mg, dapsone 100 mg, and clofazimine 100 mg. He developed ENL and RR with a significant neuritis 4 months after treatment was initiated. Daily thalidomide 100 mg and prednisone 60 mg (1 mg/kg) were started and rifampin was changed to minocycline 100 mg daily with moderate improvement of symptoms. Prednisone was slowly tapered to doses ranging from 35 mg to 15 mg daily, and 18 months after the first episode of ENL the patient developed an ENL flare. Thalidomide was increased to 200 mg daily for 1 week and then to 300 mg daily. Symptoms improved. After 2 months of being on high doses of thalidomide and prednisone (30 mg to 40 mg daily), MMF was added as a steroid sparing agent initially at 50 mg twice daily and then at 1000 mg twice daily.

Thalidomide was lowered to 250 mg nightly and several attempts to taper the dose below 40 mg were unsuccessful. Three moths later, the patient complained of persistent burning pain in his hands and feet, mostly at night. Due to this burning pain, thalidomide was stopped. Nerve conduction studies demonstrated slowing of ulnar and median motor conduction and a sensory peripheral neuropathy consistent with thalidomide neuropathy. The patient was referred to the U.S. National HD Program where he was diagnosed with a probable thalidomide neuropathy. The recommendation was to restart thalidomide in order to lower the prednisone dose. While on thalidomide 200 mg and prednisone 40 mg, his ENL recurred and the patient developed acute orchitis requiring prednisone 80 mg daily for adequate ENL control. Despite 10 months of MMF 2 grams daily, in addition thalidomide 200 mg and clofazimine 100 mg daily, his prednisone could not be lowered due to flares of lesions and symptoms.

**Case 2.** A 29-year-old Burmese man with BL HD (slit smear average of 4.3) on October 2001 presented with bilaterally enlarged tender greater auricular and ulnar nerves and pink annular plaques on elbows, knees, and the periorbital region. His RR was treated

with prednisone (1 mg/kg/day) with minimal improvement noted after 2 months. MMF 500 mg twice daily was started at 500 mg twice daily and later increased to 1000 mg twice daily. During the 7 months he was on MMF, several attempts were made to lower the prednisone dose. Each taper resulted in an exacerbation of symptoms. The MMF was discontinued.

**Case 3.** A 51-year-old Hispanic female on treatment for BL (slit smear average of 1.1) for 5 months developed a severe RR which was treated with prednisone 40 mg daily and had a good response. After several months, when prednisone was tapered to 5 mg daily, she developed a new RR. Prednisone was increased to 80 mg daily with a subsequent worsening of her diabetes mellitus. MMF 500 mg twice daily was started and then increased to 1000 mg twice daily. The patient had improved signs and symptoms. However, she developed severe gastrointestinal distress which resolved when MMF was discontinued 3 months later.

## DISCUSSION

Several drugs are available for the treatment of HD reactions, most are used in combination. Prednisone, which remains the gold standard therapy for the acute symptoms of both reactions, is fraught with numerous side effects since these leprosy reactions require many months to years of immunosuppressive therapy. Thalidomide, which is the most effective drug in the treatment of ENL, is also related to toxicities including peripheral neuropathy. Other effective drugs for ENL include high dose clofazimine, which has an anti-inflammatory effect, and pentoxifylline, which like thalidomide inhibits tumor necrosis factor-alpha (TNF-α) production.

Mycophenolate mofetil (MMF), an immunosuppressant agent, has been used in transplanted patients ([3, 7]), and also as a steroid sparing immunosuppressive in inflammatory skin diseases such as pemphigus vulgaris ([6]). MMF is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), an enzyme that is critical in the *de novo* synthesis of purines. Lymphocytes, in contrast to most other cells, depend more on the *de novo* pathway for purine synthesis than the salvage pathway. Therefore, MMF affects both B and T lymphocyte synthesis. RR is thought to be caused by increased T-cell reactivity to *Mycobacterium leprae* ([4]) although recent data suggests that humoral immunity may also be involved ([8]). ENL pathogenesis has been attributed to an increase of TNF-α syntheis which is induced by T cells ([1, 9]). These mechanisms suggested that MMF would be useful in treating RR and ENL; however, this was not observed during MMF treatment in these patients.

—Anne E. Burdick, M.D., M.P.H

*Professor of Dermatology,*
*University of Miami and Medical Director,*
*University of Miami/Jackson Memorial*
*Hospital Hansen's Disease Program*

—Claudia C. Ramirez, M.D.

*Research Fellow,*
*Department of Dermatology*
*and Cutaneous Surgery,*
*University of Miami, Miami, Florida*

## REFERENCES

1. Barnes, P. F., Chatterjee, D., Brennan, P. J., Rea, T. H., and Modlin, R. L. Tumor necrosis factor production in patients with leprosy. Infect. Immun. **60(4)** (1992) 1441–1446.
2. Barnhill, R. L., and McDougall, A. C. Thalidomide: use and possible mode of action in reactional lepromatous leprosy and in various other conditions. J. Am. Acad. Dermatol. **7(3)** (1982) 317–323.
3. Behrend, M. Mycophenolate mofetil: suggested guidelines for use in kidney transplantation. Bio.Drugs. **15(1)** (2001) 37–53.
4. Britton, W. J. The management of leprosy reversal reactions. Lepr. Rev. **69(3)** (1998) 225–234.
5. Crawford, C. L. Use of thalidomide in leprosy. Adverse Drug React. Toxicol. Rev. **13(4)** (1994) 177–192.
6. Enk, A. H., and Knop, J. Mycophenolate is effective in the treatment of pemphigus vulgaris. Arch. Dermatol. **135(1)** (1999) 54–56.
7. McDiarmid, S. V. Mycophenolate mofetil as induction therapy after liver transplantation. Liver Transpl. Surg. **5(4 Suppl 1)** (1999) S85–S89.
8. Mohanty, K. K., Joshi, B., Katoch, K., and Sengupta, U. Leprosy reactions: humoral and cellular immune responses to *M. leprae*, 65kDa, 28kDa, and 18 kDa antigens. Int. J. Lepr. Other Mycobact. Dis. **72(2)** (2004) 149–158.
9. Oliveira, R. B., Moraes, M. O., Oliveira, E. B., Sarno, E. N., Nery, J. A., and Sampaio, E. P. Neutrophils isolated from leprosy patients release TNF-alpha and exhibit accelerated apoptosis *in vitro*. J. Leukoc. Biol. **65(3)** (1999) 364–371.
10. Parikh, D. A., Ganapati, R., and Revankar, C. R. Thalidomide in leprosy—study of 94 cases. Indian J. Lepr. **58(4)** (1986) 560–566.