Clinical
paperUveitis associated with rifabutin and macrolide therapy for *Mycobacterium avium intracellulare* infection in AIDS patients

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Objective: Uveitis has been increasingly recognised as a side effect of rifabutin regimens in the prophylaxis and treatment of *Mycobacterium avium intracellulare* (MAI) infection. This study describes the clinical features and analyses the factors associated with rifabutin induced uveitis.

Design: Retrospective observational study.

Setting: Tertiary care institution, The Royal Hospitals NHS Trust, London.

Patients: 68 HIV seropositive individuals receiving rifabutin for prophylaxis or treatment of MAI infection.

Results: 11 episodes of uveitis occurred in 10 different individuals at a median of 62 days. The disease was bilateral in four and unilateral in the remainder. All subjects experienced ocular pain and photophobia and 9 individuals had a significant reduction in visual acuity. Uveitis was treated with mydriatics and topical steroids and resolved in all cases when rifabutin was stopped. The risk of uveitis was significantly increased with concurrent clarithromycin therapy, Odds Ratio 13.08, 95% Confidence Interval 1.98 to 83.12.

Conclusion: Rifabutin can cause a reversible uveitis. This risk is increased with concurrent clarithromycin therapy. Adverse drug interactions can be an important cause of morbidity in patients with advanced HIV disease.

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Keywords: Uveitis; *Mycobacterium avium intracellulare*; rifabutin; clarithromycin

Introduction

Many recent advances in the management of HIV disease stem from improved treatment and prophylaxis of opportunist infections.¹ *Mycobacterium avium intracellulare* (MAI) is one of the commonest causes of secondary opportunistic infections in AIDS, often dominating its later stages. Recognition of the associated morbidity and the development of more effective drugs against this organism have improved the survival of patients with MAI bacteraemia.²⁻³

Rifabutin, a semi-synthetic derivative of rifampicin-S, is a broad spectrum antibiotic which is particularly active against mycobacterial species. It has several similar side effects to rifampicin including nausea, vomiting, hepatotoxicity and the risk of drug interactions but apparently with lower frequency. A reversible syndrome of arthralgia and arthritis has been described and in one dose-ranging study two cases of uveitis at high doses were also noted.⁴ A recent Canadian multicentre trial using rifabutin 600 mg in combination with clarithromycin 2 g daily and ethambutol 15 mg/kg/day revealed a 40% prevalence of uveitis.⁵ In addition significantly lower rates of uveitis (1.67%) have been noted where rifabutin 300 mg was used as primary prophylaxis against MAI infection.⁶ In our practice rifabutin had been used as treatment for MAI infection for several years without any significant ocular toxicity. In 1992 clarithromycin was added to our standard rifabutin contain-

ing regimens for MAI infection. We report an outbreak of severe uveitis in a cohort of patients receiving rifabutin for prophylaxis and treatment of MAI infection and analyse factors predisposing towards this adverse event.

Methods

HIV seropositive individuals receiving rifabutin between June 1992 and April 1994 were identified. Case notes were then analysed retrospectively. All subjects were HIV-seropositive. The diagnosis of uveitis was established by ophthalmological review in all subjects but one. In the latter's case his history and the findings of circumcorneal injection, small pupils and vitreous opacities on fundoscopic examination were felt to be sufficient for a diagnosis of uveitis. Statistical analysis consisted of multi-variate analysis for each prognostic factor, chi square test (Fisher's Exact Test) and Odds Ratio (OR) with 95% confidence intervals (CI), determined by logic limits according to Cornfield.⁷

Results

Sixty eight patients received 71 treatments with rifabutin. Eleven individuals received rifabutin 300 mg as primary MAI infection prophylaxis. The MAI infection treatment regimen was rifabutin, ethambutol and clarithromycin (36 patients). The remaining patients (n = 24) consisted of three different treatment

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Table 1 MAI regimens of individuals with uveitis

	Rifabutin	Clarithromycin	Ethambutol
1	600 mg	2 g daily	15 mg/kg/day
2	600 mg	2 g daily	15 mg/kg/day
3	600 mg	1 g daily	15 mg/kg/day
4	600 mg	1 g daily	15 mg/kg/day
5	450 mg	1 g daily	15 mg/kg/day
6	450 mg	2 g daily	15 mg/kg/day
7	450 mg	2 g daily	15 mg/kg/day
8	450 mg	1 g daily	15 mg/kg/day
9	300 mg	1500 mg daily	15 mg/kg/day
10*	600 mg	1 g daily	15 mg/kg/day

*Developed second episode of uveitis on rifabutin 450 mg, ethambutol 15 mg/kg/day and fluconazole 300 mg/day. Apart from patient 3 who received 200 mg fluconazole the remaining patients were on 50 mg fluconazole a day.

groups with equal numbers. The first group were those on two drug MAI infection therapy (rifabutin and ethambutol), the second on triple therapy where azithromycin replaced clarithromycin. The third group consisted of patients in whom rifabutin was combined with standard anti-tuberculous drugs. Two thirds of patients on treatment for MAI infection received 450 mg of rifabutin with the remainder getting 600 mg. Clarithromycin 500 mg twice daily was prescribed in 27 patients and 1 g twice daily in nine. The median age of this cohort was 36 years (range 26 to 55) with 65 males and three females. Sixty were white, five black and three were Asian.

Eleven episodes of uveitis occurred in 10 patients at a median of 62 days (range 27–370) after starting treatment with rifabutin. The MAI regimens of those individuals with uveitis are given in table 1. Pain was a symptom in all episodes while visual impairment was noted in 10. In four cases visual acuity was reduced to counting fingers. The disease was unilateral in six and bilateral in four, especially in those in whom rifabutin was continued. Hypopyon was noted in three subjects. In three subjects, arthralgia occurred with uveitis. Anterior uveitis was observed in eight individuals, with panuveitis in two. There was no evidence of active cytomegalovirus (CMV) retinitis, toxoplasmosis or syphilis on clinical, ophthalmological or laboratory grounds. Investigations to exclude other causes of uveitis in these individuals included chest and sacroiliac radiology, autoantibody serology and screens for sexually transmitted diseases. Anterior chamber punctures performed on one patient revealed no bacteria, mycobacteria, fungi, or CMV. Topical steroid (dexamethasone 0.1%) and mydriatics were used in most patients. Follow up data are available for ten patients. Complete resolution of symptoms has occurred in nine cases at a median 8

Table 2 Incidence of uveitis in subjects taking rifabutin and clarithromycin compared with those on rifabutin alone or rifabutin with other anti-MAI drugs

	Uveitis	
	Yes	No
Rifabutin and clarithromycin	10	26
Rifabutin alone	1*	34
Rifabutin and other MAI therapy		

*This patient was on rifabutin 450 mg, ethambuton 600 mg and fluconazole 300 mg.

Table 3 Number of subjects who developed uveitis on clarithromycin 100 mg compared with clarithromycin 1500/2000 mg

	Uveitis	
	Yes	No
Clarithromycin 1500/2000 mg	5	4
Clarithromycin 1000 mg	5	22

days (range 5–72) after stopping rifabutin. One patient, in whom rifabutin was continued for a year after the onset of uveitis, developed bilateral cataracts. This may have been secondary to a low grade panuveitis or to topical steroid treatment.⁸ A second patient has also developed a cataract.

There was no significant relationship between the development of uveitis with age, toxoplasma serostatus, a history of non specific urethritis and CMV retinitis, liver blood tests (AST), concurrent drugs such as zidovudine, acyclovir or G-CSF. Unlike previous reports this study showed no statistical association between fluconazole and uveitis.^{6,9,10} This may well reflect the fact that the majority of patients were on 50 mg of fluconazole whereas the pharmacokinetic interaction has only been reported at doses of 200 mg. Indeed, of the six patients who were on 200 mg or more of fluconazole two developed uveitis, one of whom was the only individual not on clarithromycin (table 1). The risk of uveitis was significantly greater in patients on rifabutin in combination with clarithromycin than those on rifabutin alone or combined with other anti-mycobacterial agents (OR 13.08 95% CI 1.98–83.12, Fishers Exact Test $p = 0.007$; table 2). The association is still significant for rifabutin and clarithromycin in comparison with other rifabutin combination therapies (OR 8.85 95% CI 1.32–60.11, Fishers Exact Test $p = 0.04$). There was a trend towards significance with increasing clarithromycin doses (OR 5.50 95% CI 1.16–26.89, Fishers Exact Test $p = 0.08$ table 3).

Discussion

Uveitis in HIV disease has been described in the context of opportunist infections (*Mycobacterium tuberculosis*, syphilis, herpes zoster) and possibly secondary to HIV itself.^{11,12} Uveitis associated with rifabutin was initially noted at doses greater than 1500 mg.⁴ It was later shown to occur frequently at therapeutic doses of 600 mg in combination with clarithromycin and ethambutol.^{5,13,14} A substantially lower incidence of uveitis has been noted where rifabutin at 300 mg has been used as monotherapy in primary MAI infection prophylaxis. Although the data do not completely exclude the possibility of a new intraocular pathogen we are confident that rifabutin was the most likely cause of uveitis in this series. There was a cluster of nine cases of uveitis in a three month period in patients on therapy for MAI infection following a change in the unit's protocol for treatment of this infection. Common causes of uveitis in this age group

were not found. Only one further episode of uveitis occurred after the MAI treatment protocol was modified. A number of other factors including concurrent fluconazole and liver disease have been suggested as increasing the risk of uveitis with rifabutin.⁹ In this patient cohort the principal risk factor for rifabutin induced uveitis was concurrent clarithromycin therapy.

Clarithromycin is a member of the macrolide group of antibiotics, which can inhibit cytochrome P₄₅₀ drug metabolism. Clarithromycin can inhibit rifabutin metabolism and double the blood levels.¹⁵ This drug interaction may explain the significantly increased incidence of uveitis observed. There was a trend towards statistical significance for uveitis with increasing clarithromycin doses. Our experience with azithromycin suggests that it is less of a problem compared with clarithromycin. This difference may, however, be dose related, as all subjects received azithromycin 500 mg daily whereas higher doses were associated with uveitis in another study.⁶ Possible pathogenic mechanisms may include direct drug toxicity, Type 3 hypersensitivity reaction, Herxheimer reaction and exposure to a new intraocular pathogen (Lightman, Opremcak, Pinching, personal communication).

In conclusion we have shown that rifabutin can cause a reversible uveitis. The risk increases with the use of clarithromycin. We have changed our protocol so that 300 mg of rifabutin is prescribed with 1 g of clarithromycin. There has been only one further episode of uveitis to date. This report illustrates the hazards of adverse drug interactions from the polypharmacy frequently needed in this patient group.

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- 1 Lane HC, Laughton BE, Fallon J, Kovacs JA, Davey RT, Polis MA, *et al.* Recent advances in the management of AIDS-related opportunistic infections. *Ann Intern Med* 1994;120:945-52.
- 2 Helbert M, Robinson D, Buchanan D, Hellyer T, McCarthy M, Brown I, *et al.* Mycobacterial infection in patients infected with the human immunodeficiency virus. *Thorax* 1990;45:45-8.
- 3 Chin DP, Reingold AL, Stone EN, Vittinghoff E, Horsburgh CR, Simon EM, *et al.* The impact of *Mycobacterium avium* complex bacterium and its treatment on survival of AIDS patients—a prospective study. *J Infect Dis* 1994;170:578-84.
- 4 Siegal FP, Eilbott D, Burger H, Gehan K, Davidson B, Kaell AT, *et al.* Dose-toxicity of rifabutin in AIDS-related complex: syndrome of arthralgia/arthritis. *AIDS* 1990;4:433-41.
- 5 Shafran SD, Deschenes J, Miller M, Phillips P, Toma E. Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin, and ethambutol. MAC Study Group of the Canadian HIV Trials Network. *N Engl J Med* 1994;330:438-9.
- 6 Havlir D, Torriani F, Dube M. Uveitis Associated with Rifabutin Prophylaxis. *Ann Intern Med* 1994;121:510-2.
- 7 Armitage P, Berry G. *Statistical Methods in Medical Research*, 3rd Ed. London. Blackwell Scientific Publications.
- 8 Butcher JM, Austin M, McGilliard J, Bourke RD. Bilateral cataracts and glaucoma induced by long term use of steroid eye drops. *BMJ* 1994;308:43.
- 9 Fuller JD, Stanfield LE, Craven DE. Rifabutin prophylaxis and uveitis. *N Engl J Med* 1994;330:1315-6.
- 10 Saran BR, Maguire AM, Nichols C, Frank I, Hertle RW, Brucker AJ, *et al.* Hypopyon uveitis in patients with acquired immunodeficiency syndrome treated for systemic *Mycobacterium avium* complex infection with rifabutin. *Arch Ophthalmol* 1994;112:1159-65.
- 11 Passo MS, Rosenbaum JT. Ocular syphilis in patients with human immunodeficiency virus infection. *Am J Ophthalmol* 1988;106:1-6.
- 12 Farrell PL, Heinemann MH, Roberts CW. Response of human immunodeficiency virus associated uveitis to zidovudine. *Am J Ophthalmol* 1988;106:7-10.
- 13 Frank MO, Graham MB, Wispelway B. Rifabutin and uveitis. *N Engl J Med* 1994;330:868.
- 14 Jacobs DS, Piliero PJ, Kuperwaser MG, Smith JA, Harris SD, Flanagan TP, *et al.* Acute uveitis associated with rifabutin used in patients with human immunodeficiency virus infection. *Am J Ophthalmol* 1994;118:717-22.
- 15 The DATRI 001 Study Group. Coadministration of clarithromycin (CL) alters the concentration, time profile of rifabutin (RFB). 34th Interscience conference on antimicrobial agents and chemotherapy. Orlando, October 1994 A2 [abstract].