NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

COMMUNICABLE DISEASES SURVEILLANCE BULLETIN

VOLUME 12. NO 1 APRIL 2014

FOREWORD

Resistance to the antimicrobial rifampicin is a key marker for multidrug-resistant tuberculosis (MDR-TB) and is an emerging concern. The increasing incidences of MDR-TB and alternative therapy possibilities are discussed in this issue, which also includes details of laboratory confirmed human rabies in South Africa for the period 2012-2013. Cases of rabies occur annually in South Africa despite the availability of effective control and prevention measures.

Surveillance reports for this issue include the four influenza surveillance programmes that are co-ordinated by the NICD. Data on milder influenza-like illness (ILI) and severe acute respiratory (SARI) illness, collated for 2013, show that the 2013 influenza season was initially dominated by circulation of influenza A(H1N1)pdm09 followed by A(H3N2) in the latter part of the season. The surveillance data also show that the 2013 season was unusually protracted. Antimicrobial resistance surveillance is also conducted at the NICD, and aims to determine the extent of resistance amongst the most important disease causing pathogens in South Africa. Data presented in this issue show the extent of antimicrobial resistance by pathogen for 2012.

All contributors are thanked for their inputs, and I trust you will find these reports useful and interesting.

Basil Brooke, Editor

CONTENTS

DEVELOPMENT OF RESISTANCE TO RIFAMPICIN AND OTHER RIFAMYCINS IN MYCOBACTERIUM TUBERCULOSIS AND THE EXTENT OF CROSS-RESISTANCE BETWEEN THESE ANTIMICROBIALS

Nazir Ismail, Andries Dreyer, Hendrik Koornhof

Centre for Tuberculosis, NICD

Introduction

The rifamycin class of antimicrobial agents was discovered in *Streptomyces mediterranei* (now *Nocardia mediterranei*) in 1957.[1] Rifampicin, first evaluated during clinical trials in 1967[1], is used globally for the treatment of tuberculosis. Together with isoniazid, rifampicin is the cornerstone of combination treatment for drug-susceptible tuberculosis. It is also used in combination

with dapsone for the treatment of paucibacillary leprosy, and these two drugs plus clofazimine are used to treat multibacillary leprosy.[2] Rifampicin combined with doxycycline is recommended by WHO for the treatment of brucellosis while rifampicin combined with either ofloxacin or doxycycline has also been shown to be effective for the treatment of brucellosis with the caveat that fluoroquinolone should not be used on its own.[3] Rifampicin also shows good anti-staphylococcal activity and has been used in combination with an aminoglycoside and/or vancomycin for the treatment of *Staphylococcus epidermidis* endocarditis involving prosthetic valves.[4] Experimental infections in animal models of *S. epidermidis* endocarditis showed that the combination of rifampicin and a fluoroquinolone was superior to treatment with vancomycin alone.[5] Other rifamycins available for clinical use or evaluated in clinical trials are rifabutin, rifapentine and rifalazil.

Mode of action of rifamycins

Rifampicin binds to the β-subunit of the DNA-dependent RNA polymerase enzyme encoded by the *rpoB* gene and in the process inhibits transcription and therefore protein synthesis in rifampicin susceptible organisms.

Genetic basis of resistance to rifamycins

The genetic basis of resistance to rifampicin and other rifamycins in *Mycobacterium tuberculosis,* the causative agent of tuberculosis, involves alterations (insertion, deletion or missense mutations) in the 81-bp rifampicin resistance determining region (RRDR), located in the central part of the *rpoB* gene.[6-10]

Cross-resistance involving rifamycins

Various degrees of rifamycin cross-resistance involving rifampicin, rifabutin, rifapentine or rifalazil (KRM- 1648) can occur.[10,11] Single nucleotide mutations involving codons 531 and 513 confer resistance to all four rifamycins, while mutations in codon 516 are associated with resistance to rifampicin and rifapentine only, leaving susceptibility to rifabutin and rifalazil intact.[6,12] In Australia, low frequency *rpoB* mutations at codon 522 encode resistance to rifampicin but do not appear to affect susceptibility to rifabutin.[13] Mutations in codon 526 confer resistance to rifampicin and rifapentine alone (glutamic acid or leucine substitutions) or to all four rifamycins (tyrosine substitution).[12]

Mutations encoding different levels of rifamycin resistance

Missense mutations in codons 516, 526 (some mutations) or 531 result in high-level rifampicin resistance and mutations at position 514, 517, 521, 526 (some mutations), or 533 are associated with low-level resistance.[6,11-13]

Global extent of rifampicin resistance in *Mycobacterium tuberculosis*

Rifampicin resistance is a key marker of multidrug-resistant (MDR) – tuberculosis and is an emerging concern. Based on reports from countries world-wide, WHO estimated that 83,715 patients were diagnosed globally with MDR-tuberculosis in 2012.[14] This is likely an under-estimate as drug susceptibility testing is not universally applied, especially in the developing world and true estimates are likely above 300,000. In South Africa, a total of 13,915 new MDR cases were diagnosed in 2012. This is slightly higher than the 13,762 new MDR cases reported in 2011.

Discussion

Amongst the armamentarium of drugs used in the treatment of chronic infections, the advent of rifamycins has changed the landscape of antimicrobial therapy, most notably rifampicin for the treatment of tuberculosis and leprosy and, to a lesser extent, rifabutin for the treatment and prophylaxis of *Mycobacterium avium* complex infections in patients with AIDS. However, due

to the increasing incidence of resistance to rifampicin coupled with resistance to isoniazid, leading to multi-drug resistant tuberculosis (MDR-TB), emphasis has shifted towards alternative tuberculosis therapies. Amongst these, at least theoretically following clinical validation, could be drug regimens containing rifabutin or rifalazil for infections caused by strains harbouring *M. tuberculosis* isolates with mutations in codons 516 or 522, as well as some strains with codon 526 mutations in the *rpoB* gene.

Rifampicin is consistently integrated into phenotypic drug susceptibility panels, but other rifamycins are not. Therefore, considerations could be given to the use of *M. tuberculosis* genetic profiles to predict cross-resistance patterns so as to enable the treatment of tuberculosis caused by some rifampicin-resistant strains, including some mono-resistant cases, which carry mutations associated with susceptibility to rifabutin and rifalazil, e.g. isolates with codon 516 or 522 mutations. Treatment with rifabutin has an additional benefit of fewer drug interactions in patients receiving protease inhibitors as part of anti-retroviral therapy. Furthermore, the performance of minimum inhibitory concentration (MIC) testing of strains could aid the interpretation of the genotypic findings for patient management.

Conclusion

Many unanswered questions remain with regard to the use of rifamycins for the effective treatment of resistant strains of tuberculosis. However, the use of phenotypic and genotypic methods to demonstrate levels of resistance and cross-resistance can optimize and prolong their usage.

References

1. Sensi P. History of the development of rifampin. *Rev Infect Dis* 1983; 5: S402–S406
2. Williams DL, Gillis TP. Drug-resistant leprosy: monitoring and current status. *Lepr Rev* 2012; 83: 269-281
3. Akova M, Uzun D, AkalinHE, et al. Quinolones in the treatment of human brucellosis; Comparative trial of ofloxacin-rifampin versus doxyclycline-rifampin. *Antimicrob Agents Chemother* 1993; 37: 1831-1834
4. Karchmer AW, Archer GL, Dismukes WE. *Staphylococcus epidermidis* causing prosthetic valve endocarditis: Microbiologic and clinical observations as guides to therapy. *Ann Intern Med* 1983; 98: 447-455
5. Rouse MS, Wilcox SM, Henry NK, et al. Ciprofloxacin therapy of experimental endocarditis caused by methicillin-resistant *Staphylococcus epidermidis. Antimicrob Chemother* 1990; 34: 273-376
6. Ramaswamy S, Musser JM. Molecular genetic basis of antimicrobial agent resistance in *Mycobacterium tuberculosis:* 1998 update. *Tuber Lung Dis* 1998; 79: 3-29
7. Miller IP, Crawford JT, Shinnick TM. The *rpoB* gene of *Mycobacterium tuberculosis. Antimicrob Agents Chemother* 1994; 38: 805-811.
8. Musser JM. Antimicrobial agent resistance in mycobacteria: molecular genetic insights. *Clin Microbiol Rev* 1995; 8: 496-514.
9. Telenti AP, Imboden F, Marchesi D, Lowrie S, Cole MJ. Colston L, Matter K, Schopfer K, Bodmer T. Detection of rifampicin-resistance mutations in *Mycobacterium tuberculosis. Lancet* 1993; 34: 647-650.
10. Williams DL, Wagnespack C, Eisenach K, Crawford JT, Portaels F, Salfinger CM, Nolan C, Abe C, Stich-Groh V, Gillis TP. Characterization of rifampin resistance in pathogenic mycobacteria. *Antimicrob Agents Chemother*. 1994; 38: 2380- 2386.
11. Williams DL, Spring L, Collins I Miller LP, Heifets LB, Gangadharam PRJ, Gillis TP. Contribution of *rpoB* mutations to development of rifamycin cross-resistance in *Mycobacterium tuberculosis. Antimicrob Agents Chemother* 1998; 42: 1853-1857.
12. Saribaş Z, Kogagöz T, Alp A, Günalp A. Rapid detection of rifampicin resistance in *Mycobacterium tuberculosis* isolates by heteroduplex analysis and determination of rifamycin cross-resistance in rifamycin-resistant isolates. *J Clin Microbiol* 2003; 41:816-818
13. Sintchenko V, Chew WK, Jelfs PJ, Gilbert GL. Mutations in *rpoB* gene and rifabutin susceptibility of multidrug-resistant Mycobacterium *tuberculosis* strains isolated in Australia. *Pathology* 1999; 31: 275-264
14. WHO. Global tuberculosis report. Geneva, World Health Organization, 2013. http:www.who.int/publications/global_report/en/ (accessed March 24, 2014).