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Activities of a New Oral Streptogramin, XRP 2868, Compared to Those of Other Agents against *Streptococcus pneumoniae* and *Haemophilus* Species

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MIC methodology was used to test the antibacterial activity of XRP 2868, a new oral combination of two semisynthetic streptogramins, RPR 132552A and RPR 202868, compared to activities of other antibacterial agents against pneumococci, *Haemophilus influenzae*, and *Haemophilus parainfluenzae*. For 261 pneumococci, XRP 2868 and pristinamycin MICs were similar, irrespective of penicillin G and erythromycin A susceptibilities (MIC at which 50% of isolates were inhibited [MIC_{50}], 0.25 μg/ml; MIC_{90}, 0.5 μg/ml), while quinupristin/dalfopristin had MICs which were 1 to 2 dilutions higher. Single components of both XRP 2868 and quinupristin/dalfopristin had higher MICs. Erythromycin A, azithromycin, clarithromycin, and clindamycin MICs were higher for penicillin G-intermediate and -resistant than -susceptible pneumococci. Against 150 *H. influenzae* strains, all compounds tested had unimodal MIC distributions. XRP 2868 had an overall MIC_{50} of 0.25 μg/ml and an MIC_{90} of 1.0 μg/ml, with no differences between β-lactamase-positive, β-lactamase-negative, and β-lactamase-negative ampicillin-resistant strains. Of note was the similarly low activity of one of its components, RPR 132552A. Pristinamycin and quinupristin/dalfopristin had MICs of 0.125 to 8.0 μg/ml; quinupristin alone had MICs of 8.0 to >64.0 μg/ml, and dalfopristin had MICs of 1.0 to >64.0 μg/ml. Erythromycin A, azithromycin, and clarithromycin had modal MICs of 4.0, 1.0, and 8.0 μg/ml, respectively. MICs of all compounds against *H. parainfluenzae* were 1 to 2 dilutions higher than against *H. influenzae*. XRP 2868 showed potent activity against pneumococci and *Haemophilus* strains irrespective of their susceptibility to other agents.

The major bacterial pathogens responsible for community-acquired respiratory tract infections comprise *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (6, 7, 9–11, 24). Pneumococcal resistance to penicillin G and other β-lactam and non-β-lactam compounds has increased worldwide at an alarming rate, including in the United States. Major foci of resistance prevalence currently include South Africa, Spain, Japan, Hong Kong, Korea, and Central and Eastern Europe (2, 4, 10, 11). In the United States, a recent survey (4) showed an increase in penicillin G nonsusceptibility from <5% before 1989 (including <0.02% of isolates for which MICs were ≥2.0 μg/ml) to 6.6% in 1991 to 1992 (for 1.3% of isolates, MICs were ≥2.0 μg/ml). In another, more recent survey, 50.4% of 1,476 clinically significant pneumococcal isolates were not susceptible to penicillin G (11). Previous studies have shown that parenteral quinupristin/dalfopristin and oral pristinamycin (available in France) are very potent against pneumococci, irrespective of their β-lactam and erythromycin A susceptibilities (8, 12, 15, 19, 21). It is also important to note the high rates of isolation of penicillin G-intermediate and -resistant pneumococci (approximately 30%) in middle ear fluids from patients with refractory otitis media, compared to other isolation sites (3). The problem of drug-resistant pneumococci is compounded by the ability of resistant clones to spread from country to country and from continent to continent (2, 10, 16).

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Although *H. influenzae* remains a major cause of respiratory tract infections (24), *Haemophilus parainfluenzae* may also play a role, especially in acute exacerbations of chronic bronchitis (20). The major resistance mechanism of these species is β-lactamase (TEM-1 or ROB-1) production, the prevalence of which is approximately 40% in the United States (11). The incidence of β-lactamase-negative ampicillin-resistant (BLNAR) strains is currently <1% in the United States (11) but is significantly higher in Japan (23). Among members of the macrolide and azalide groups, azithromycin has the lowest MICs against these organisms, followed by ketolides such as telithromycin, erythromycin A, and clarithromycin (1, 5, 6, 10, 14, 17). Of available streptogramins, oral pristinamycin and parenteral quinupristin/dalfopristin have MICs for *H. influenzae* and *H. parainfluenzae* which are several dilutions higher than those for pneumococci (8, 12, 15). The exact therapeutic role of the macrolide-azalide group in therapy of *H. influenzae* infections is unclear (11), and pristinamycins have not been used for this purpose.

There is an urgent need for oral compounds for outpatient treatment of otitis media and other respiratory tract infections caused by penicillin G-intermediate and -resistant pneumococci (7) as well as *H. influenzae*. Available groups include β-lactams, macrolides, and quinolones. Oral pristinamycin is not available in the United States, and quinupristin/dalfopristin can be administered only parenterally.

XPR 2868 is a new investigational oral streptogramin, being a 70/30 ratio of RPR 132552A and RPR 20868 (Fig. 1). The present study tested (i) the activities of XPR 2868, RPR 132552A, RPR 20868, pristinamycin, quinupristin/dalfopristin,

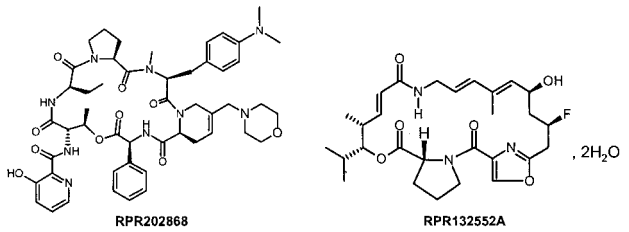

FIG. 1. Structures of the components of XRP 2868. XRP 2868 consists of a 30/70 combination of RPR 202868 (a pristinamycin I_A derivative) and RPR 132552A (a pristinamycin II_B derivative).

quinupristin, dalfopristin, erythromycin A, azithromycin, clarithromycin, and clindamycin against 261 pneumococci by agar dilution MIC testing and (ii) the activities of all of the latter compounds except clindamycin against 150 *H. influenzae* and 26 *H. parainfluenzae* strains by microdilution MIC testing. This is the first journal publication on this compound of which we are aware.

MATERIALS AND METHODS

Bacteria. Pneumococci comprised 86 penicillin G-susceptible (MICs, ≤0.06 μg/ml), 81 penicillin G-intermediate (MICs, 0.125 to 1.0 μg/ml), and 94 penicillin G-resistant (MICs, 2.0 to 16.0 μg/ml) strains. Of these, 120 were erythromycin resistant (MICs, ≥1.0 μg/ml); 65 had *erm*(B), 32 had *mef*(A), 1 had *erm*(B) and *mef*(A), 19 had mutations in L4, and 3 had mutations in 23S rRNA (A2059G). These macrolide-resistant strains were relatively recent clinical isolates (1998 to 2002) with previously defined phenotypes and genotypes from our collection.

One hundred fifty *H. influenzae* and 26 *H. parainfluenzae* strains were tested. *H. influenzae* strains comprised 146 recent untypeable isolates and 4 type b strains from our collection. β-Lactamase testing was performed by the Cefinase (BBL Microbiology systems, Cockeysville, Md.) disk method.

Antibacterials and MIC testing. All drug substances were obtained from Aventis Pharma, Romainville, France. The agar dilution method, as used in our laboratory for many years (10, 11, 13, 17, 21, 22), was performed for pneumococci by using Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.) supplemented with 5% sheep blood. Standard quality control strains, including *S. pneumoniae* ATCC 49619 (18), were included in each run of agar dilution MICs. Plates were incubated in air for 20 to 24 h.

For *Haemophilus* strains, MICs were determined by the NCCLS microdilution method (18) using commercially prepared frozen panels (TREK, Inc., Cleveland, Ohio) using freshly prepared *Haemophilus* test medium. Inocula were prepared from chocolate agar plates incubated a full 24 h by the direct colony suspension method as recommended by the NCCLS. Standard quality controls were used on each day of testing. Inoculum checks were also performed, and only trays yielding 3×10^5 to 7×10^5 CFU/ml were used. Trays were covered and incubated overnight at 35°C in ambient air (11).

RESULTS

Results of agar dilution MICs with pneumococcal strains classified by penicillin G susceptibility are summarized in Table 1, and results for strains classified by erythromycin A susceptibility are found in Table 2. XRP 2868, pristinamycin, and quinupristin/dalfopristin had low MICs irrespective of the strain's penicillin G or erythromycin A susceptibility status, with MICs ranging from 0.06 to 1.0 μg/ml (XRP 2868), 0.125 to 1.0 (pristinamycin), and ≤0.06 to 1.0 (quinupristin/dalfopristin) μg/ml. The two components of XRP 2868 and quinupristin/dalfopristin were without significant activity. Streptogramin MICs for macrolide-resistant strains were not influenced by erythromycin A resistance mechanisms. Macrolide MICs for ribosomal mutants were higher than those for the wild type, as published previously (13). However, streptogramin MICs were uninfluenced by macrolide susceptibility status or resistance mechanisms.

MICs of erythromycin A, azithromycin, clarithromycin, and clindamycin for pneumococci rose with those of penicillin G.

TABLE 1. Agar dilution MICs for 261 pneumococcal strains classified by penicillin susceptibility

Drug and strain category (*n*)[a]	MIC (μg/ml)		
	Range	50%	90%
Penicillin G			
Penicillin S (86)	0.016–0.06	0.03	0.03
Penicillin I (81)	0.125–1.0	0.25	1.0
Penicillin R (94)	2.0–16.0	2.0	4.0
XPR 2868			
Penicillin S	0.06–0.25	0.125	0.25
Penicillin I	0.06–0.5	0.25	0.25
Penicillin R	0.06–1.0	0.25	0.5
RPR 132552			
Penicillin S	<0.5–16.0	4.0	8.0
Penicillin I	≤0.5–64.0	4.0	8.0
Penicillin R	≤0.5–>64.0	4.0	32.0
RPR 202868			
Penicillin S	≤0.5–>64.0	4.0	16.0
Penicillin I	1.0–>64.0	8.0	32.0
Penicillin R	1.0–>64.0	16.0	64.0
Pristinamycin			
Penicillin S	0.125–0.5	0.25	0.25
Penicillin I	0.125–1.0	0.25	0.5
Penicillin R	0.125–1.0	0.25	0.5
Quinupristin/dalfopristin			
Penicillin S	≤0.06–1.0	0.5	0.5
Penicillin I	0.125–1.0	0.5	1.0
Penicillin R	0.125–1.0	0.5	1.0
Quinupristin			
Penicillin S	≤0.5–64.0	2.0	4.0
Penicillin I	≤0.5–>64.0	4.0	32.0
Penicillin R	≤0.5–>64.0	4.0	32.0
Dalfopristin			
Penicillin S	8.0–>64.0	64.0	>64.0
Penicillin I	8.0–>64.0	64.0	>64.0
Penicillin R	16.0–>64.0	>64.0	>64.0
Erythromycin A			
Penicillin S	0.016–>64.0	0.125	32.0
Penicillin I	0.03–>64.0	0.125	>64.0
Penicillin R	0.03–>64.0	>64.0	>64.0
Azithromycin			
Penicillin S	0.03–>64.0	0.125	16.0
Penicillin I	0.06–>64.0	0.125	>64.0
Penicillin R	0.06–>64.0	>64.0	>64.0
Clarithromycin			
Penicillin S	≤0.008–>64.0	0.03	8.0
Penicillin I	0.016–>64.0	0.06	>64.0
Penicillin R	≤0.008–>64.0	32.0	>64.0
Clindamycin			
Penicillin S	≤0.008–>64.0	0.06	0.06
Penicillin I	0.016–>64.0	0.06	>64.0
Penicillin R	0.016–>64.0	0.06	>64.0

[a] S, susceptible; I, intermediate; R, resistant.

TABLE 2. Agar dilution MICs for 261 pneumococcal strains classified by erythromycin A susceptibility

Drug and strain category (*n*)[a]	MIC (μg/ml)		
	Range	50%	90%
Penicillin G			
Erythromycin S (141)	0.016–4.0	0.125	2.0
Erythromycin R (120)	0.016–16.0	1.0	4.0
XRP 2868			
Erythromycin S	0.06–0.25	0.125	0.25
Erythromycin R	0.06–1.0	0.25	0.5
RPR 132552			
Erythromycin S	≤0.5–16.0	4.0	8.0
Erythromycin R	≤0.5–>64.0	4.0	32.0
RPR 202868			
Erythromycin S	≤0.5–32.0	4.0	8.0
Erythromycin R	2.0–>64.0	16.0	64.0
Pristinamycin			
Erythromycin S	0.125–0.5	0.25	0.25
Erythromycin R	0.125–1.0	0.25	0.5
Quinupristin/dalfopristin			
Erythromycin S	≤0.06–1.0	0.5	0.5
Erythromycin R	0.25–1.0	0.5	1.0
Quinupristin			
Erythromycin S	≤0.5–8.0	2.0	4.0
Erythromycin R	1.0–>64.0	8.0	64.0
Dalfopristin			
Erythromycin S	8.0–>64.0	64.0	>64.0
Erythromycin R	8.0–>64.0	>64.0	>64.0
Erythromycin A			
Erythromycin S	0.016–0.25	0.06	0.125
Erythromycin R	1.0–>64.0	>64.0	>64.0
Azithromycin			
Erythromycin S	0.03–0.25	0.125	0.125
Erythromycin R	1.0–>64.0	>64.0	>64.0
Clarithromycin			
Erythromycin S	≤0.008–0.125	0.03	0.06
Erythromycin R	0.25–>64.0	>64.0	>64.0
Clindamycin			
Erythromycin S	≤0.008–0.125	0.06	0.06
Erythromycin R	0.016–>64.0	1.0	>64.0

[a] S, susceptible; R, resistant.

Lower clindamycin MICs for erythromycin A-resistant strains reflected the presence of *mef* genes and ribosomal protein mutations; such strains were clindamycin susceptible. Complete cross-resistance occurred between erythromycin A, azithromycin, and clarithromycin.

Of the 150 *H. influenzae* strains, 79 produced β-lactamase. Of the 26 *H. parainfluenzae* strains, 8 were β-lactamase positive. Twenty-one of the 71 β-lactamase-negative *H. influenzae* strains were ampicillin resistant (MICs, ≥1.0 μg/ml) and were classified as BLNAR. Microdilution MICs are presented in Tables 3 and 4. There were no significant differences in MICs based upon β-lactamase production, ampicillin resistance, or serotype. MICs of all compounds had a unimodal distribution, with MICs at which 50% of strains were inhibited (MIC_{50}s)

TABLE 3. MICs for *H. influenzae*

Drug	MIC (μg/ml)											
	β-Lactamase-negative strains (*n* = 50)			β-Lactamase-positive strains (*n* = 79)			BLNAR strains (*n* = 21)			All strains (*n* = 150)		
	Range	50%	90%	Range	50%	90%	Range	50%	90%	Range	50%	90%
XRP 2868	≤0.06–1.0	0.25	0.5	≤0.06–1.0	0.25	1.0	≤0.06–1.0	0.25	0.5	≤0.06–1.0	0.25	1.0
RPR 132522	0.12–1.0	0.25	0.5	0.12–1.0	0.25	0.5	0.12–>8.0	0.25	0.5	0.12–>8.0	0.25	0.5
RPR 202868	2.0–>64	>64	>64	2.0–>64	>64	>64	2.0–>64	>64	>64	2.0–>64	>64	>64
Pristinamycin	0.5–2.0	1.0	2.0	0.12–4.0	1.0	2.0	0.25–4.0	1.0	1.0	0.12–4.0	1.0	2.0
Quinupristin/dalfopristin	1.0–8.0	2.0	4.0	0.25–8.0	4.0	4.0	1.0–8.0	2.0	4.0	0.25–8.0	2.0	4.0
Quinupristin	16–>64	32	>64	8.0–>64	32	>64	16–>64	64	>64	8.0–>64	32	>64
Dalfopristin	1.0–8.0	2.0	8.0	1.0–32	4.0	8.0	1.0–>64	2.0	4.0	1.0–>64	2.0	8.0
Erythromycin	2.0–16	4.0	8.0	0.5–16	4.0	8.0	1.0–16	4.0	8.0	0.5–16	4.0	8.0
Azithromycin	0.5–2.0	1.0	2.0	0.12–2.0	1.0	2.0	0.5–8.0	1.0	2.0	≤0.12–8.0	1.0	2.0
Clarithromycin	4.0–32	8.0	16	1.0–64	8.0	8.0	4.0–16	4.0	16	1.0–64	8.0	16.0

TABLE 4. MICs for *H. parainfluenzae*

Drug	MIC (μg/ml)								
	β-Lactamase-negative strains (n = 18)			β-Lactamase-positive strains (n = 8)			All strains (n = 26)		
	Range	50%	90%	Range	50%	90%	Range	50%	90%
XRP 2868	0.12–2.0	1.0	2.0	0.12–4.0	1.0	1.0	0.12–4.0	1.0	2.0
RPR 132552	0.06–2.0	0.5	2.0	20.06–4.0	1.0	1.0	≤0.06–4.0	0.5	2.0
RPR 202868	>64–>64	>64	>64	>64–>64	>64	>64	>64–>64	>64	>64
Pristinamycin	0.5–8.0	4.0	4.0	1.0–8.0	4.0	4.0	0.5–8.0	4.0	4.0
Quinupristin/dalfopristin	1.0–16	8.0	16	2.0–32	8.0	16	1.0–32	8.0	16
Quinupristin	32–>64	>64	>64	32–>64	>64	>64	32–>64	>64	>64
Dalfopristin	1.0–32	8.0	16	1.0–32	8.0	16	1.0–32	8.0	16
Erythromycin	1.0–8.0	2.0	4.0	1.0–8.0	4.0	4.0	1.0–8.0	2.0	4.0
Azithromycin	0.25–2.0	0.5	1.0	0.25–1.0	0.5	1.0	0.25–2.0	0.5	1.0
Clarithromycin	2.0–16	4.0	8.0	2.0–16	8.0	16	2.0–16	4.0	16

and MIC_{90}s (in micrograms per milliliter) as follows: XRP 2868, 0.25 and 1.0; RPR 132552A, 0.25 and 0.5; RPR 202868, >64.0 and >64.0; pristinamycin, 1.0 and 2.0; quinupristin/dalfopristin, 2.0 and 4.0; quinupristin, 32.0 and >64.0; dalfopristin, 2.0 and 8.0; erythromycin A, 4.0 and 8.0; azithromycin, 1.0 and 2.0; clarithromycin, 8.0 and 16.0. MICs of all compounds for *H. parainfluenzae* were generally 1 to 2 dilutions higher than those for *H. influenzae*, and unimodal distributions were observed.

DISCUSSION

XPR 2868 is a new oral streptogramin composed of two semisynthetic synergistic components in a 70/30 (wt/wt) association: RPR 132552A (group A streptogramin) and RPR 202868 (group B streptogramin). The antibacterial spectrum of XPR 2868 includes gram-positive cocci, fastidious gram-negative rods involved in respiratory tract infections, and anaerobes. As with all other streptogramins (19), the compound is rapidly bactericidal, with a postantibiotic effect against pneumococci of 0.05 to 4.35 h, depending upon MIC and exposure time. XPR 2868 also selects for resistant mutants of *Staphylococcus aureus* in vitro at lower rates than other compounds tested (J. C. Barriere, E. Bacque, N. Berthaud, G. Dutruc-Rooset, G. Doerflinger, and G. Puchault, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-359, 2001; N. Berthaud, N. Diallo, B. Prevost, S. Lannier-Bonnamour, A. De Usatorre, and J. Hodgson, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-360, 2001; S. Dutka Malen, N. Berthaud, V. Boisrobert, F. Efremenko, A. M. Gouin, J. Martin, J. Rousseau, and J. Hodgson, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-361, 2001; S. Dutka Malen, N. Berthaud, O. Sergent, and J. Hodgson, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-362, 2001; L. M. Kelly, M. R. Ednie, A. Jacobs, A. Bryskier, C. Couturier, and P. C. Appelbaum, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-1667, 2002). The MICs for both pneumococci and *H. influenzae* with XPR 2868 obtained in this study were similar to those reported above in preliminary studies.

Previous studies (8, 12, 15) have documented excellent activity of quinupristin/dalfopristin against macrolide-susceptible and -resistant pneumococci, with MICs similar to those obtained in the present study. Neither component of the combination alone had significant antipneumococcal activity. Approximately 10 years ago, an oral streptogramin, RPR 106972, was briefly evaluated but was not further developed. In preliminary studies (22), RPR 106972 MICs were similar to those of XRP 2868, with no significant activity of the two constituent components of either compound. Pristinamycin was also very active against all groups of pneumococci (22). As has been reported by others (11), macrolide resistance, and to a lesser extent clindamycin resistance, increased with that of penicillin G in our study. MICs of XRP 2868 and pristinamycin were usually 1 to 2 dilutions lower than those of quinupristin/dalfopristin.

Our results show that XRP 2868 had low MICs (≤1.0 μg/ml) for all *H. influenzae* strains tested, with slightly higher MICs for *H. parainfluenzae*. It is noteworthy that RPR 132552A, one of the two components of XRP 2868, alone was as effective as the combination against all strains. In all susceptible species, the two components of XRP 2868 act synergistically (Barriere et al., 41st ICAAC; Berthaud et al., 41st ICAAC; Dutka Malen et al., 41st ICAAC, abstr. F-361; Dutka Malen et al., 41st ICAAC, abstr. F-362; Kelly et al., 42nd ICAAC; A. Bryskier, personal communication). Quinupristin/dalfopristin and pristinamycin had MICs which were 2 to 3 dilutions higher than those of XRP 2868 and RPR 132552A (8, 15), while the macrolides yielded their usual unimodal distributions (11).

In summary, XRP 2868, a new oral streptogramin, had low MICs for all pneumococcal and *Haemophilus* strains tested, regardless of their susceptibilities to other agents. Pharmacokinetic/pharmacodynamic and toxicity studies are warranted before clinical evaluation of this compound can occur.

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