Asian Journal of Pharmacy and Life Science ISSN 2231 – 4423
Vol.3 (1), Jan-March, 2013

PROMISING REGIMEN IDOL FOR MENINGITIS TREATMENT DUE TO *S. PNEUMONIA* RESISTANT STRAINS

Sawati Sharma[*1], Parul Sood[1]

School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences & Technology, Makhnumajra, Baddi, Distt. Solan-173205, H.P, India

***Corresponding Author's Email:** swatisharma713@gmail.com

ABSTRACT

The resistance of S. pneumoniae to antibiotics led to the beginning of a restless search in quest of a sole therapy that could be used as an empirical therapy in all resistant strains. Monotherapies have already been proved to be ineffective for the treatment of bacterial meningitis due to resistant strains, thus a combination of drug is often a drug of choice. Combination of ceftriaxone and vancomycin persists to be the first drug of choice combination as empirical therapy, although different combinations of drugs are tested in order to find a better regimen than this combination. Co-administration of dexamethasone as adjuvant therapy decreases the permeability of the BBB that is compensated by reducing the effectiveness of the drug, thereby hampering the treatment. The emergence of multidrug resistance drove the development and evaluation of quinolones as new anti-pneumococcal agents. In future, a combination of β-lactam antibiotics and quinolones might play a central role in the empirical treatment of bacterial meningitis. Since, the degree of antibiotic resistance continues to increase and change, the strategies for managing these infections need to be modified in response to the resistance in S. pneumoniae.

KEYWORDS *Cephalosporin, CSF, penicillin, resistant strains and S. pneumoniae.*

INTRODUCTION

Meningitis caused by *Streptococcus pneumoniae,* is the most frequent disease infecting adults as well as children. About 26.3% of fatality rate is associated with bacterial meningitis. Bacterial meningitis still remains a serious disease, despite improvement in the antimicrobial therapy [1]. Earlier penicillin was the only drug of choice, but, due to occurrence of resistance, newer therapeutic ranges of antibiotics came into existence [2]. Penicillin and other β-lactams inhibit cell-wall synthesis by binding to the penicillin-binding proteins (PBPs), which are responsible for cell wall maintenance. Emergence of resistance among *S. pneumoniae* to penicillins and other β-lactams occurs after several sequences of chromosomally mediated mutations of the five high–molecular weight PBPs (1A, 1B, 2B, 2X, and 3) whereas, β-lactamase is not produced by the pneumococci thus making it clear that it is not responsible for causing resistance [3]. Alterations in the PBP enzymes led to a reduced affinity among the PBP and the β-lactam drug [4]. The prevalence of antibiotic resistance for *S. pneumoniae* and its mechanism have been the subject of numerous reviews and is beyond the scope of this review, thus will not be discussed further [5-7]. It is interesting to note that an empirical therapy that could be used to treat bacterial meningitis due to resistant strains is still a work in the progress. But in the quest of an appropriate drug or drug combination a large number of studies have been carried out. The question is whether the antibiotics combinational therapy is preferred over monotherapy or a single drug can serve the purpose alone. This review aims in compiling the studies that have been carried out with combination of various antibiotics in *S. pneumoniae* induced meningitis and to deduce whether monotherapy or combination should be the first choice of antibiotic therapy.

The various agents that are used to treat the antibiotic resistant strains of *S. pneumoniae* can be summarized as follows:

Agents used to treat penicillin resistant strains:

Penicillin resistant strains of *S. pneumoniae* are the ones that have MIC >1 μg/mL whereas the relatively resistant strains have MICs of 0.1 to 1.0 μg of penicillin per Ml [8]. Gouveia1 *et al.,* (2011) examined the impact of penicillin resistance on outcomes of pneumococcal meningitis over a period of ten years in infectious diseases hospital in Brazil. Findings from this study emphasized the use of third generation cephalosporins for the treatment of suspected pneumococcal meningitis even at low prevalence of pneumococcal resistance to penicillin [9], but the efficacy of ceftriaxone was assessed by McCracken *et al.,* (1985) against a relatively penicillin resistant pneumococcal strain (MBC 8.0 μg/mL) and efficacy of ceftriaxone, vancomycin and imipenem against a penicillin-resistant strain. Finding from the study revealed that penicillin G and ceftriaxone reduced the number of organisms in cerebrospinal fluid by 4.14 logl0 CFU/mL after single doses and after 9 h continuous infusions. While in the case of infection due to a penicillin-resistant strain, a single dose of penicillin or ceftriaxone failed to lower the number of organisms in CSF. Imipenem and Vancomycin reduced the count in CSF by at least 4.10 and 2.19 $\log_{l0}$ CFU/ml after single doses and 9 hr infusions, respectively thus it might prove to be effective for the therapy [8].

Despite its good penetration in the CSF, gentamicin was inferior to vancomycin monotherapy against penicillin resistant pneumococci. On the other hand the combination of the two showed significant results when compared to monotherapies [10].

Contrary to the reports in the above studies due to the narrow therapeutic window of vancomycin, strict monitoring of its serum levels is required and the variability of its levels in CSF the routine use of vancomycin in adults for treating penicillin-resistant pneumococcal meningitis should not be recommended. Viladrich *et al.,* (1991) reported that out of the 11 adults with pneumococcal meningitis treated with vancomycin and early adjunctive therapy including dexamethasone, 4 patients experienced a therapeutic failure that led to change in vancomycin therapy. [11] Due to the variability of vancomycin level in CSF Ian *et al.,* (1993) conferred that vancomycin therapy within 10hrs of treatment resulted in a mean reduction of 3.0 $\log_{10}$ CFU/mL in bacterial concentration, but after 14 h regrowth occurred [12].

It is noteworthy that ceftriaxone and meropenem were least effective as monotherapy reported in the same study. The combination of rifampin with either ceftriaxone or vancomycin was not more effective than single-agent therapy. By contrast vancomycin and ceftriaxone were synergistic, suggesting that the combination might be effective for initial empiric therapy of pneumococcal meningitis [12].

Meropenem, a broad-spectrum carbapenem, was bactericidal in rabbit model of meningitis due to highly resistant strain of penicillin (MIC 4 μg/mL) reported by Gerbera *et al.,* (1999), and was insignificantly superior to ceftriaxone and vancomycin. Although the combination of vancomycin with ceftriaxone was more active than ceftriaxone alone. On the other hand an insignificant gain was observed by the addition of vancomycin to meropenem [13].

Kim *et al.,* (2004) evaluated the therapeutic efficacy of meropenem and compared various treatment regimens in a rabbit model of meningitis caused by penicillin-resistant *Streptococcus pneumoniae*. The therapeutic efficacy of meropenem and vancomycin in combination and in comparison to that of Ceftriaxone and Vancomycin that was contrary to the results obtained from Gerbera *et al.,* (1999). It was inferred that the meropenem monotherapy may not be a suitable choice for penicillin resistant meningitis, while combination of meropenem and vancomycin could serve to be a possible alternative in the treatment of penicillin resistant strains meningitis [14].

Cefepime a broad-spectrum fourth generation cephalosporin, showed excellent penetration and bactericidal activity in the inflamed meninges that was superior to the monotherapies of ceftriaxone and vancomycin. The above results

qualified Cefepime as a potential candidate in cases where broad antibacterial activity is required for the treatment of pneumococcal meningitis; it can serve the purpose alone or in combination with vancomycin [15].

Fernandez *et al.,* (2005) reported Teicoplanin; a glycopeptide alone was very effective in animal model of cephalosporin-resistant pneumococcal meningitis but when used in combination not alone. Synergism was reported between the ceftriaxone and vancomycin in vitro, but no synergism was reported in animal models [16].

The penetration of gemifloxacin into the inflamed meninges was 22 to 33% in rabbit model of meningitis, it produced bactericidal activity that was better than that of standard regimen i.e. ceftriaxone and vancomycin against penicillin resistant strain [17].

Addition of cefotaxime to levofloxacin not only showed synergistic effect in-vitro against penicillin resistant strains, but it also suppressed the resistance induced due to levofloxacin by the mutation of the genes encoding topoisomerase IV and gyrase [18]. Against pneumococci that are susceptible to β-lactams, rifampin appears to be considerably less active than ceftriaxone [19]. Clinafloxacin alone and in combination with teicoplanin and rifampin was ineffective against strains resistant to penicillin and ciprofloxacin and neither did the combination worked [20]. In penicillin sensitive strains of *S. pneumoniae* ceftriaxone was less effective than moxifloxacin when administered in high concentration, thus qualifying it to be a potential therapy for the treatment of the disease [21].

Agents used to treat cephalosporin resistant strains:

Klugman (1994) reported the failure of cefotaxime and ceftriaxone in treating the resistant strains that has led to the revision in the breakpoint for pneumococcal resistance to cefotaxime and ceftriaxone [22]. On account of failure reports of extended spectrum cephalosporin, Klugman *et al.,* (1995) assessed the cerebrospinal fluid of children with bacterial meningitis; ceftriaxone alone was unable to kill intermediately ceftriaxone resistant or fully resistant strains at CSF concentration of 5μg/mL. Although at higher concentrations bactericidal activity was present. The addition of vancomycin or rifampin to ceftriaxone significantly enhanced CSF bactericidal activity in comparison to that of ceftriaxone alone. The study led to the conclusion that ceftriaxone and any similar agents were not relevant for the treatment of cephalosporin resistance in pneumococci [23].

Using the same antibiotics Ribes *et al.,* (2005) assessed there *in vitro* and *in vivo* efficacy alone and combined against *S. pneumoniae* ATCC 51916 (a strain that is characterized by high resistance levels to ceftriaxone/cefotaxime (MICs of 32 mg/L) and an intermediate penicillin resistance). Ceftriaxone combined with rifampicin or vancomycin produced an effect that was statistically significant when compared to ceftriaxone alone as reported earlier by Klugman (1995), whereas, rifampicin and vancomycin did not produce any significant alterations in the activity of either drug alone, but was more effective than ceftriaxone. Inflammatory data obtained with rifampicin confirmed its low potential for inducing a CSF inflammatory response, and that the addition of rifampicin or vancomycin to ceftriaxone led to reduction in inflammatory parameters in comparison to ceftriaxone monotherapy [24].

Fosfomycin, a broad-spectrum antibiotic acting by inhibiting the first step of cell wall synthesis, was assessed by Ribes *et al.,* (2006), against two strains of *S. pneumoniae*: HUB 2349 (fosfomycin and ceftriaxone, MICs 16 and 2 mg/L) and ATCC 51916 (MICs of 4 and 32 mg/L) alone and in combination with ceftriaxone and vancomycin. Once again the combination with either of the two showed improved efficacy and there was decrease in the inflammatory response due to the combination over monotherapy. Thus, qualifying the combinations as a possible alternative in allergic condition or cases where intolerance to first-line drugs occurs [25].

Other non β lactam antibiotics used as therapy:

Non β-lactam antibiotics with anti pneumococcal activity, such as rifampicin or quinolones, have proven effective in the animal model of meningitis and have emerged as possible alternatives especially for patients allergic to penicillin

or for infections with strains with very high cephalosporin resistance. [25]. The progressive spread of pneumococcal resistant clones to antibiotics promoted the use of fluoroquinolones for its management. Therefore, fluoroquinolones such as moxifloxacin, gatifloxacin, levofloxacin and gemifloxacin with antipneumococcal activity may play a significant role in the management of pneumococcal disease [26]. Fluoroquinolones have emerged as the drug of choice as prevalence of resistance among *S. pneumoniae* to these drugs have been reported to be 0.3% that is relatively low in comparison to resistance due to other antibiotics, although there are potentials for unrecognized resistance that can occur [27].

Addition of cefotaxime to levofloxacin not only showed synergistic effect *in vitro* against penicillin resistant strains, but it also suppressed the resistance induced due to levofloxacin by the mutation of the genes encoding topoisomerase IV and gyrase [18].

Strains of *S. pneumoniae* with MIC of 0.008 μg/mL for rifampin, 0.5μg/mL for ofloxacin and 0.03μg/mL for ceftriaxone was used in an experiment conducted on rabbit model, result from the study revealed the ineffectiveness of rifampin exhibited diminished bactericidal activity thus not making rifampicin an optimal antibiotic. When combined to ofloxacin the two did not show any synergism [19].

Egermann *et al.,* (2009) stated the combination of daptomycin with ceftriaxone was the most efficacious regimen for treatment of pneumococcal meningitis [28]. The advent of strains of pneumococcus that are resistance to vancomycin lead to the evaluation of garenoxcin and moxifloxacin, the two agents proved to be more efficacious as monotherapies than Ceftriaxone and vancomycin in combination in meningitis caused due to the strains having vancomycin tolerance [29].

The combination of cefotaxime and levofloxacin immensely decreased the risk of tolerance to quinolones. [18] Meningitis due to tolerated stains of ciprofloxacin rendered the use of clinafloxacin alone and in combination with teicoplanin and rifampin ineffective for its management [20].

Dexamethasone as an adjuvant therapy hampers the effectiveness of drug therapy:

Sensorineural hearing loss (SNHL) is the most common after effect of bacterial meningitis and is observed in 30% of survivors when the disease is caused by *S. pneumoniae*. Meningitis is the single most important origin of acquired SNHL in childhood. Anti-inflammatory dexamethasone holds promises as potential adjuvant therapy to prevent SNHL associated with meningitis. [30] It has been reported in many studies that the use of an adjuvant therapy decreases the entry of the antibiotic in the CSF as it interferes with the permeability of the BBB and showed decreased penetration of drug in CSF thus decreasing the efficacy of therapy studied by Fernandez *et al.,* (2005) [31].

Egermann *et al.,* (2009) inferred that the penetration of daptomycin was remarkably decreased to 2% from 6% by the addition of dexamethasone. In the same study it was deduced that the addition to ceftriaxone and vancomycin rendered the regimen completely ineffective for the treatment [28]. The same was reported with the addition of teicoplanin, although therapeutic failure did not occur [31].

CONCLUSION

S. pneumoniae being a pervasive and problematic pathogen around the globe because of its resistance to penicillin and other classes of antimicrobials, none of the anti-microbial agents currently available for clinical use is ideal as single-agent therapy for resistant pneumococcal meningitis strains. Ceftriaxone and vancomycin still persists to be the first choice of drug combination as empirical therapy. Various *in vitro* and *in vivo* studies have been conducted on animal model qualify many non β-lactam antibiotics as a potential therapeutic option for the treatment of meningitis, especially when resistant strains are involved. On the other hand addition of adjuvant therapy reduces the entry of antibiotics in the CSF and hampers the effectiveness of drug therapy. In the future, a combination of β-lactam

antibiotics and quinolones might play a central role in the empirical treatment of bacterial meningitis. Although, these results deserve further evaluation and caution must be exercised in applying results from the animal model to the management of patients. Since the degree of antibiotic resistance continues to change and increase, the approach to managing these infections must be modified in response to these changes

REFERENCES

1. Tunkel A.R., Scheld W.M.. Pathogenesis and pathophysiology of bacterial meningitis. Clin Microbiol Rev. 1993. 6: 118-36.
2. Kaplan, S.L., Mason E.O. Jr. Management of infections due to antibiotic-resistant Streptococcus pneumoniae. Clin Microbiol Rev. 1998. 11: 628-44.
3. Reichmann P., Konig A., Linares J., Alcaide F., Tenover F.C., Dougal Mc. L. A global gene pool for high level cephalosporin resistance in commensal Streptococcus species and Streptococcus pneumoniae. J Infect Dis. 1997. 176: 1001-12.
4. Markiewicz Z., Tomasz A.. Variation in penicillin-binding protein patterns of penicillin-resistant clinical isolates of pneumococci. J Clin Microbiol. 1989. 27: 405-10.
5. Klugman K..P.. Pneumococcal resistance to antibiotics. Clin Microbiol Rev.1990. 3: 171-96.
6. Butler J.C., Hofmann J., Cetron M.S., Elliott J.A., Facklam R.R., Breiman R. F.. The Pneumococcal Sentinel Surveillance Working Group. The continued emergence of drug-resistant Streptococcus pneumoniae in the United States: an update from the Centers for Disease Control and Prevention Pneumococcal Sentinel Surveillance System. J Infect Dis. 1996. 174: 986-93.
7. Appelbaum P.C.. Resistance among Streptococcus pneumoniae: Implications for drug selection. Clin Infect Dis. 2002. 34: 1613-20.
8. Cracken G.H. Mc., Sakata Y. Jr. Antimicrobial therapy of experimental meningitis caused by Streptococcus pneumoniae strains with different susceptibilities to penicillin. Antimicrob Agents Chemother. 1985. 27: 141-5.
9. Gouveia E.L., Reis J.N., Flannery B., Cordeiro S.M., Lima J.B., Pinheiro R.M.. Clinical outcome of pneumococcal meningitis during the emergence of pencillin-resistant Streptococcus pneumoniae: an observational study. BMC Infect Dis. 2011. 11: 323.
10. Cottagnoud P., Gerber C.M., Cottagnoud M., Tauber M.G.. Gentamicin Increases the Efficacy of Vancomycin against Penicillin-Resistant Pneumococci in the Rabbit Meningitis Model. Antimicrob Agents Chemother. 2002. 46: 188-90.
11. Viladrich P.F., Gudiol F., Linares J., Pallares R., Sabate I., Rufi G.. Evaluation of Vancomycin for Therapy of Adult Pneumococcal Meningitis. Antimicrob Agents Chemother. 1991. 35: 2467-72.
12. Friedland I.R., Paris M., Ehrett S., Hickey S., Olsen K., McCracken G.H. Jr.. Evaluation of Antimicrobial Regimens for Treatment of Experimental Penicillin- and Cephalosporin-Resistant Pneumococcal Meningitis. Antimicrob Agents Chemother. 1993. 37: 1630-6.
13. Gerber C.M., Cottagnoud M., Neftel K.A., Tauber M.G., Cottagnoud P.. Meropenem alone and in combination with vancomycin in experimental meningitis caused by a penicillin-resistant pneumococcal strain. Eur J Clin Microbiol Infect Dis. 1999. 18: 866-70.
14. Kim S.W., Jin J.H., Kang S.J., Jung S.I., Kim Y.S, Kim C.K.. Therapeutic Efficacy of Meropenem for Treatment of Experimental Penicillin-Resistant Pneumococcal Meningitis. J Korean Med Sci. 2004. 19: 21-6.

15. Gerber C.M., Cottagnoud M., Neftel K., Tauber M.G., Cottagnoud P.. Evaluation of cefepime alone and in combination with vancomycin against penicillin-resistant pneumococci in the rabbit meningitis model and in vitro. J Antimicrob Chemother. 2000. 45: 63-8.
16. Fernandez A., Cabellos C., Tubau F., Maiques J.M., Domenech A., Ribes S.. Experimental study of teicoplanin, alone and in combination, in the therapy of cephalosporin-resistant pneumococcal meningitis. J Antimicrob Chemother. 2005. 55: 78-83.
17. Smirnov A., Wellmer A., Gerber J., Maier K., Henne S., Nau R.. Gemifloxacin Is Effective in Experimental Pneumococcal Meningitis. Antimicrob Agents Chemother. 2000. 44: 767-70.
18. Kuhn F., Cottagnoud M., Acosta F., Flatz L., Entenza J., Cottagnoud P.. Cefotaxime acts synergistically with levofloxacin in experimental meningitis due to penicillin-resistantpneumococci and prevents selection of levofloxacin resistant mutants in vitro. Antimicrob Agents Chemother. 2003. 47: 2487-91.
19. Nau R., Kaye K.., Sachdeva M., Sande E.R., Tauber M.G.. Rifampin for therapy of experimental peumococcal meningitis in rabbits. Antimicrob Agents Chemother. 1994. 38: 1186-9.
20. Domenech A., Cabellos C., Ribes S., Tubau F., Viladrich P.F., Linares J.. Microbial Drug Resistance Experimental Study of Clinafloxacin Alone and in Combination in the Treatment of Ciprofloxacin-Susceptible and -Resistant Pneumococcal Meningitis. Microb Drug Resist. 2003. 9 Suppl 1: S53-9.
21. Schmidt H., Dalhoff A., Stuertz K., Trostdorf F., Chen V., Schneider O.. Moxifloxacin in the Therapy of Experimental Pneumococcal Meningitis. Antimicrob Agents Chemother. 1998. 42: 1397-407.
22. Klugman K.P.. Pneumococcal resistance to the third-generation cephalosporins: clinical, laboratory and molecular aspects. Int J Antimicrob Agents. 1994. 4: 63-7.
23. Klugman K.P., Friedland I.R., Bradley J.S.. Bactericidal activity against cephalosporin-resistant Streptococcus pneumoniae in cerebrospinal fluid of children with acute bacterial meningitis. Antimicrob agents chemother. 1995. 39: 1988-92.
24. Ribes S., Taberner F., Domenech A., Cabellos C., Tubau F., Linares J.. Evaluation of ceftriaxone, vancomycin and rifampicin alone and combined in an experimental model of meningitis caused by highly cephalosporin-resistant Streptococcus pneumoniae ATCC 51916. J Antimicrob Chemother. 2005. 56: 979-82.
25. Ribes S., Taberner F., Domenech A., Cabellos C., Tubau F., Linares J.. Evaluation of fosfomycin alone and in combination with ceftriaxone or vancomycin in an experimental model of meningitis caused by two strains of cephalosporin-resistant Streptococcus pneumoniae. J. Antimicrob Chemother. 2006. 57: 931-6.
26. Touyama M., Higa F., Nakasone C., Shinzato T., Akamine M., Haranaga S.. In vitro activity of sitafloxacin against clinical strains of Streptococcus pneumoniae with defined amino acid substitutions in QRDRs of gyrase A and topoisomerase IV. J Antimicrob Chemother. 2006. 58: 1279-82.
27. Wortmann G.W., Bennett S.P.. Fatal Meningitis Due to Levofloxacin-Resistant Streptococcus pneumoniae. Clin Infect Dis. 1999. 29: 1599-600.
28. Egermann U., Stanga Z., Ramin A., Acosta F., Stucki A., Gerber P.. Combination of daptomycin plus ceftriaxone is more active than vancomycin plus ceftriaxone in experimental meningitis after addition of dexamethasone. Antimicrob Agents Chemother. 2009. 53: 3030-3.
29. Rodriguez-Cerrato V., McCoig C.C., Saavedra J., Barton T., Michelow I.C., Hardy R.D.. Garenoxacin (bms-284756) and moxifloxacin in experimental meningitis caused by vancomycin-tolerant pneumococci. Antimicrob Agents Chemother. 2003. 47: 211-5.

30. Coimbra R.S., Loquet G., Leib S.L.. Limited efficacy of adjuvant therapy with dexamethasone in preventing hearing loss due to experimental pneumococcal meningitis in the infant rat. Pediatr Res. 2007. 62: 291-4.
31. Fernandez A., Cabellos C., Tubau F., Maiques J.M., Domenech A., Ribes S.. Experimental study of teicoplanin, alone and in combination, in the therapy of cephalosporin-resistant pneumococcal meningitis. J Antimicrob Chemother. 2005. 55: 78-83.