Intensive Care Med (2004) 30:343–346
DOI 10.1007/s00134-003-2135-y

EDITORIAL

Malina Ioanas
Hartmut Lode

Linezolid in VAP by MRSA: a better choice?

Received: 27 November 2003
Accepted: 18 December 2003
Published online: 6 February 2004

M. Ioanas · H. Lode (✉)
Department of Chest and Infectious Diseases,
City Hospital Emil von Behring, Free University of Berlin,
Zum Heckeshorn 33, 14109 Berlin, Germany
e-mail: haloheck@zedat.fu-berlin.de
Tel.: +49-30-80022222
Fax: +49-30-80022623

Introduction

Ventilator-associated pneumonia (VAP) is one of the most representative conditions of the contemporary pathology related to hospitalisation, invasive therapeutic devices and aggressive antibiotic use. With an incidence of 8–28% among ICU patients and an attributable mortality ranging largely between 14 and 47% [1] according to the underlying pathology, VAP has been extensively investigated over the past decade. One of the cornerstones of this condition is an early and adequate antibiotic treatment, which has proven to reduce mortality [2] and length of ICU stay [3], as well as to prevent resistance emergence [4].

In their contribution to "Intensive Care Medicine", Kollef et al. provide interesting information on the clinical cure and mortality rates in ventilator-associated pneumonia by Gram-positive organisms under treatment with linezolid or vancomycin [5]. This study represents a retrospective analysis of 544 VAP cases extracted from two previous clinical trials including, respectively, 396 and 623 patients with nosocomial pneumonia [6, 7]. When only MRSA cases were taken into account, linezolid was associated with significantly higher rates of clinical cure (62.2 vs 21.2%; p=0.001), survival (84.1 vs 61.7%; p=0.02) and eradication (60.5 vs 22.9%; p=0.001), compared with vancomycin. Facing these striking differences, some compulsory questions arise: (a) Why are we (still) treating MRSA with vancomycin? and (b) Who is to blame for its modest antimicrobial efficacy?

The first suspect: multi-drug resistant *S. aureus*

Microorganism's resistance to antibiotics is the most common reason for failure to cure an infection. Methicillin-resistant *S. aureus* is accumulating evidence concerning mechanisms of resistance acquisition, spreading, clinical outcome, and urges for new therapeutic tools. *S. aureus* showed an increasing resistance to methicillin over the past four decades, approaching 55% in United States [8] and 59.6% in Europe [9]. The prevalence of MRSA in VAP represents approximately 50% of the episodes due to *S. aureus* [1], which is the leading microorganism responsible for nosocomial pneumonia, isolated in 20–31.7% of cases [1, 10]. *S. aureus*-related mortality appears to be significantly higher in patients with VAP by MRSA (RR 20.7; 95% CI 2.78–154.35) [11] and MRSA bacteremia (OR 1.93; 95% CI 1.54–2.42; p<0.01) [12], although MRSA strains are not more virulent than the susceptible isolates. Melzer et al. [13] showed recently that in 815 patients with nosocomial *S. aureus* bacteremia, the rates of disseminated infection were similar for MRSA and MSSA (7.1 vs 6.2%; p=0.6), whereas the attributable mortality rate was significantly higher in patients infected by MRSA (11.8 vs 5.1%; p<0.001).

The MRSA strains have the particularity to develop multiple antibiotic resistance, such as up to 80% macrolide resistance and 90% quinolone resistance [14]. Furthermore, the intensive use of glycopeptide as the only therapeutic option for MRSA during the past years has led to the emergence of isolates with reduced susceptibility to vancomycin (VISA/VRSA) and teicoplanin. Glycopep-

tide-intermediate *S. aureus* (GISA) are selected by long-term glycopeptide usage but also by beta-lactams and fluoroquinolones [15].

Since the first strain with reduced susceptibility to vancomycin has been reported in Japan in 1996, approximately 21 resistant strains have been identified worldwide, the majority being actually GISA isolates, with a MIC<32 mg/l [16]. The first documented case of VRSA (vancomycin MIC>128 mg/l and teicoplanin MIC 32 μg/l), containing the *van*A vancomycin resistance gene presumably transferred from enterococci, was described in 2002 in the United States [17]. This strain, although resistant to glycopeptide and beta-lactams, was susceptible to several antibiotics such as trimethoprim/sulphamethoxazole, which was actually used for treating the patient. Another phenomenon recently described is the hetero-VRSA, a precursor strain with low vancomycin MIC (MIC≤4 mg/l), which contains a subpopulation of cells with intermediate susceptibility (MIC between 4 and 32 mg/l) that acquires full resistance under vancomycin treatment [18], although this hypothesis has not been proven by in vitro experiments [19]. The prevalence of hVISA is extremely variable, ranging between 0% (USA) and 20% (Japan), depending on definition and methodology [16]. Because its detection is encompassed by technical difficulties, the real prevalence of vancomycin-resistant strains is probably higher but still is far from being the main responsible factor for treatment failure. Although a higher attributable mortality has been reported in patients with hVISA compared with those infected by vancomycin susceptible MRSA (63 vs 12% in a study by Fridkin et al. [20] and, respectively, 85.5 vs 70% in a retrospective study on surgical patients [21]), the actual minimal incidence of VISA/GISA cannot be the only causative factor of vancomycin inefficacy.

Indeed, the studies by Rubinstein et al. [6] and Wunderink et al. [7], which were providing the data for the analysis by Kollef et al. [5], do not mention any baseline resistance of *S. aureus* to vancomycin nor new resistance acquisition during treatment with vancomycin. These findings support the hypothesis of actual lack of impact of vancomycin resistance in the treatment failure. Other factors should be responsible.

The real suspect: vancomycin, a modest drug

Treatment with vancomycin has been a continuous subject of debate concerning pharmacodynamics, dosage, monitoring, administration and toxicity. Cruciani et al. reported in 1996 that 1 h i.v. infusion of 1 g dose of vancomycin does not achieve sustained lung concentration above MIC for susceptible staphylococci over 12 h, recommending a different modality of administration [22]. Subsequently, Wysocki et al. compared continuous vs intermittent infusion of vancomycin in ICU patients with severe MRSA infection; except for some costs considerations, no differences were found in terms of microbiological or clinical outcome, pharmacokinetics or safety [23]. The need for constant treatment monitoring to maintain the optimal serum levels and to prevent toxicity has also been a negative point of this drug. In a recent editorial, Goldstein and Kitzis mentioned that approximately 40% of patients treated with vancomycin at standard dose (1 g twice daily) have inadequate serum levels [24]. Combining this information with the fact that vancomycin concentration in the epithelial lining fluid does not exceed 20% of the plasma levels [25], the overall conclusion is that penetration of vancomycin into different lung compartments is extremely poor.

Furthermore, there is a variety of situations that may explain the low efficacy of vancomycin treatment, especially in pulmonary infections. Some combinations of vancomycin with other largely used antibiotics (aminoglycosides, beta-lactams) appears to be antagonistic [24]. The presence of a high inoculum of organisms, such as in abscesses, decreases the efficacy of vancomycin because of the non-specific affinity trapping. Foreign devices, such as catheters, are also responsible for a reduced activity of vancomycin, especially against GISA, and their removal improves the clinical course [21].

Therapy of resistant staphylococci: present and perspective

At present, there is sufficient evidence that vancomycin is no longer a recommendable therapeutic option for pulmonary infections, especially when MRSA is involved.

Linezolid, the first licensed member of a new class of antibiotics, the oxazolidinones, is probably a better alternative of vancomycin, due to its activity against Gram-positive microorganisms, including MRSA and GISA, and good penetration in lung compartments [26].

However, the study by Stevens et al. [27] on 460 patients with MRSA infection, including skin infection, pneumonia, urinary tract infection and bacteremia, found no statistical differences between linezolid and vancomycin with respect to clinical cure (73 vs 73.1%) or eradication (60.7 vs 63.2%) rates. The cases of pneumonia (n=64 patients with confirmed MRSA infection at baseline) had similar trends. In contrast, the recent analysis of Wunderink et al. [28] shows a clear advantage of linezolid in patients with nosocomial pneumonia by MRSA (ITT=160, including patients with VAP analysed by Kollef et al. [5]) regarding the clinical cure rate (59% in linezolid group vs 35.5% in vancomycin group; p<0.01) and the survival rate (85% in linezolid group vs 67% in vancomycin group; p=0.05). These differences may be explained in part by the fact that the study by Stevens et al. was not powered exclusively for pneumonia, and secondly, that infections other than pneumonia

may have a better course under treatment simply because drug penetration (i.e., vancomycin) in the respective tissues is better than in the lung—which has been demonstrated for one decade already [22, 25]; thus, one can speculate that the clear superiority of linezolid in pneumonia studies is largely due to the poor efficacy of the comparator. Nevertheless, there is already evidence of linezolid-resistant strains of *S. aureus* in the USA and UK [29, 30], stressing the point that this highly active drug should be used, however, with caution, despite the optimistic results of Kollef et al. [5].

Quinupristin/dalfopristin is a semisynthetic parenteral streptogramin with activity against most of Gram-positive pathogens. A multicentre study compared quinupristin/dalfopristin and vancomycin in the treatment of nosocomial pneumonia by Gram-positive pathogens [31]. Similar clinical success rates were observed, including for MRSA subgroup, although very low (30.9% in quinupristin/dalfopristin group vs 44.4% in vancomycin group, in the bacteriologically evaluable population; n=38), suggesting that quinupristin/dalfopristin is probably not a better option than vancomycin in these patients. Furthermore, quinupristin/dalfopristin resistant strains of *S.aureus* have been already reported, even in MRSA [32].

Tigecycline, a member of glycylcyclines, which are novel tetracycline analogues with activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria, appears to be a very active antibiotic, not only on MRSA but also on glycopeptide-resistant enterococci and GISA. It is currently under phase-III clinical-trial evaluation, including nosocomial pneumonia.

To prevent or to treat?

Since sooner or later any antibiotic against *S. aureus* or other organisms is supposed to become ineffective, mainly because of resistance development and/or intrinsic pharmacodynamic limitations, parallel strategies to cope with infection must be adopted. Prevention of the increasing resistance of *S. aureus* has been shown to be a feasible approach. Antibiotic rotation and restricted use of antibiotics, increasing compliance in hygiene measures and cohorting of nurses, have favourable results in diminishing antibiotic-selective pressure and in decreasing infections by resistant *S.aureus* [33, 34]. Moreover, these measures are probably cheaper than any new antibiotic and, in addition, their chance to develop "resistance" is minimal.

References

1. Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903
2. Kollef MH, Sherman G, Ward S, Fraser VJ (1999) Inadequate antimicrobial treatment of infections. A risk factor for hospital mortality among critically ill patients. Chest 115:462–474
3. Dupont H, Mentec H, Sollet JP, Bleichner G (2001) Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. Intensive Care Med 27:355–362
4. Grusson D, Hilbert G, Vargas F, Valentino R, Bebear C, Allery A, Benissar G, Cardinaud JP (2000) Rotation and restricted use of antibiotics in a medical intensive care unit. Am J Respir Crit Care Med 162:837–843
5. Kollef MH, Rello J, Cammarata SK, Cross-Dabrera RV, Wunderink RG (2004) Clinical cure and survival in Gram-positive ventilator-associated pneumonia. Retrospective analysis of two double-blind studies comparing linezolid with vancomycin. Intensive Care Med (http://dx.doi.org/10.1007/s00134-003-2088-1)
6. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG, and the Linezolid Nosocomial Pneumonia Study Group (2001) Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis 32:402–412
7. Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH (2003) Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. Clin Ther 25:980–992
8. National Nosocomial Infections Surveillance (NNIS) System Report (2001) Data summary from January 1992 to June 2001, issued August 2001. Am J Infect Control 29:404–421
9. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M (1995) The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. J Am Med Assoc 274:639–644
10. Spencer RC (1996) Predominant pathogens found in the European Prevalence of Infection in Intensive Care Study. Eur J Clin Microbiol Infect Dis 15:281–285
11. Rello J, Torres A, Ricart M, Valles J, Gonzalez J, Artigas A, Rodriguez-Roisin R (1994) Ventilator-associated pneumonia by *Staphylococcus aureus*. Comparison of methicillin-resistant and methicillin-sensitive episodes. Am J Respir Crit Care Med 150:1545–1549
12. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y (2003) Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis 36:53–59
13. Melzer M, Eykyn SJ, Gransden WR, Chinn S (2003) Is Methicillin-resistant *Staphylococcus aureus* more virulent than methicillin-susceptible *S. aureus*? A comparative cohort study of British patients with nosocomial infection and bacteremia. Clin Infect Dis 37:1453–1460
14. EARSS Annual Report 2001. http://www.earss.rivm.nl

15. Cui L, Murakami H, Kuwahara-Arai K, Hanaki H, Hiramatsu K (2000) Contribution of a thickened cell wall and its glutamine nonamidated component to the vancomycin resistance expressed by *Staphylococcus aureus* Mu50. Antimicrob Agents Chemother 44:2276–2285
16. Walsh TR, Howe RA (2002) The prevalence and mechanisms of vancomycin resistance in *Staphylococcus aureus*. Annu Rev Microbiol 56:657–675
17. Centers for Disease Control and Prevention (2002) *Staphylococcus aureus* resistant to vancomycin. Morb Mortal Wkly Rep 51:565–567
18. Hiramatsu K, Aritaka N, Hanaki H, Kawasaki S, Hosoda Y, Hori S, Fukuchi Y, Kobayashi I (1997) Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. Lancet 350:1670–1673
19. Turner J, Howe RA, Wootton M, Bowker KE, Holt HA, Salisbury V, Bennett PM, Walsh TR, MacGowan AP (2001) The activity of vancomycin against heterogenous vancomycin-intermediate methicillin-resistant *Staphylococcus aureus* explored using in vitro pharmacokinetic model. J Antimicrob Chemother 48:727–730
20. Fridkin SK, Hageman JC, McDougal L, Mohammed J, Kellum ME et al. (2001) Nationwide epidemiologic study of *Staphylococcus aureus* with reduced susceptibility to vancomycin. The 41st Interscience Conference Antimicrobial Agents and Chemotherapy. ASM, Chicago
21. Ariza J, Pujol M, Cabo J, Pena C, Fernandez N et al. (1999) Vancomycin in surgical infections due to methicillin-resistant *Staphylococcus aureus* with heterogenous resistance to vancomycin. Lancet 353:1587–1588
22. Cruciani M, Gatti G, Lazzarini L, Furlan G, Brocalli G, Malena M, Franchini C, Concia E (1996) Penetration of vancomycin into human lung tissue. J Antimicrob Chemother 35:865–871
23. Wysocki M, Delatour F, Faurisson F, Rauss A, Pean Y, Misset B, Thomas F, Timsit JF, Similowski T, Mentec H, Mier L, Dreyfuss D, and the Study Group (2001) Continuous versus intermittent infusion of vancomycin in severe staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother 45:2460–2467
24. Goldstein FW, Kitzis MD (2003) Vancomycin-resistant *Staphylococcus aureus*: no apocalypse now. Clin Microbiol Infect 9:761–765
25. Lamer C, de Beco V, Soler P, Calvat S, Fagon JY, Dombret MC, Farinotti R, Chastre J, Gibert C (1993) Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. Antimicrob Agents Chemother 37:281–286
26. Conte JE, Golden JA, Kipps J, Zurlinden E (2002) Intrapulmonary pharmacokinetics of Linezolid. Antimicrob Agents Chemother 46:1475–1480
27. Stevens DL, Herr D, Lampiris H, Hunt JL, Batts DH, Hafkin B, and the Linezolid MRSA Study Group (2002) Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Clin Infect Dis 34:1481–1490
28. Wunderink RG, Rello J, Cammarata SK, Cross-Dabrera RV, Kollef MH (2003) Linezolid vs vancomycin. Analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Chest 124:1789–1797
29. Tsiodras S, Gold HS, Sakoulos G, Eliopoulos GM, Wennerstern C, Venkataraman L (2001) Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. Lancet 358:207–208
30. Wilson P, Andrews JA, Charlesworth R, Walesby R, Singer M, Farrell DJ et al. (2003) Linezolid resistance in clinical isolates of *Staphylococcus aureus*. J Antimicrob Chemother 51:186–188
31. Fagon JY, Patrick H, Haas DW, Torres A, Gibert C, Cheadle WG, Falcone RE, Anholm JD, Paganin F, Fabian TC, Lilienthal F, and the Nosocomial Pneumonia Group (2000) Treatment of Gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dancomycin. Am J Respir Crit Care Med 161:753–762
32. Malbruny B, Canu A, Bozdogan B, Fantin B, Zarrouk V, Dutka-Malen S (2002) Resistance to quinupristin-dalfopristin due to mutation of L22 ribosomal protein in *Staphylococcus aureus*. Antimicrob Agents Chemother 46:2200–2207
33. Raymond DP, Pelletier SJ, Crabtree TD, Gleason TG, Hamm LL, Pruett TL, Sawyer RG (2001) Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. Crit Care Med 29:1101–1108
34. Grundmann H, Hori S, Winter B, Tami A, Austin DJ (2002) Risk factors for the transmission of methicillin-resistant *Staphylococcus aureus* in an adult intensive care unit: fitting a model to the data. J Infect Dis 185:481–488