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Temocillin in cystic fibrosis: A retrospective pilot study ☆

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Abstract

Background: Temocillin is currently used in the treatment of acute pulmonary exacerbations caused by *Burkholderia cepacia* complex and multi-resistant *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients despite little published clinical data. This study assessed if intravenous (IV) antibiotic therapy including temocillin was equivalent to standard combination therapy for an acute exacerbation.
Methods: A retrospective, pilot cross-over study. Adult patients attending two CF centres between 1997 and 2006 who had received a course of IV antibiotics including temocillin (TIV) and a further IV course (within ±1 year) which did not include temocillin (NTIV) were included. Outcome measures at the start and end of each IV course were recorded (FEV_1%, FVC%).
Results: Twenty six patients had received temocillin. Baseline values of FEV_1% predicted were comparable for both groups (TIV: 37(18%), NTIV: 39(20%)). FEV_1% increased by 7.12(11.67)% after TIV ($p<0.01$) and 6.65(7.62)% after NTIV ($p<0.01$). There was no significant difference between the IV courses in mean %change in lung function TIV versus NTIV (FEV_1 0.46% [95%CI: −4.55 to 5.48%]).
Conclusion: These data suggest equivalence in the lung function outcome of IV antibiotic therapy includingtemocillin versus standard IV antibiotic therapy.
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Keywords: Temocillin; *Burkholderia cepacia* complex; *Pseudomonas aeruginosa*

1. Introduction

Temocillin is a semi-synthetic 6-alpha-methoxy derivative of ticarcillin which is highly stable to most bacterial beta-lactamases [1–5]. The spectrum of temocillin is directed towards aerobic Gram-negative bacteria but has no useful in-vitro activity against anaerobes, Gram-positive bacteria and most Gram-negative non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. [6]. This natural resistance of non-fermenters has been attributed to an inability of the molecule to enter the outer membrane of the cell wall [7–10]. Temocillin does not disturb the gastrointestinal flora, it is non-toxic, and well tolerated. Moreover antagonism against other antimicrobials is rare which may be due to the failure of temocillin to induce beta-lactamase production [11–15]. Temocillin is suitable for twice daily intravenous (IV) administration which enhances acceptability and makes it a popular choice when patients are given IV antibiotics at home [16].

Despite its spectrum temocillin has been used in cystic fibrosis (CF) to treat exacerbations in severe lung disease, particularly in patients infected with *Burkholderia cepacia*

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complex and multi-resistant *P. aeruginosa*. Indeed, a synergistic effect against *P. aeruginosa* has been shown in-vitro when temocillin is used in combination with aminoglycoside antibiotics, and temocillin has shown high in-vitro activity against *B. cepacia* complex organisms, in comparison to other beta-lactams [14,17,18]. Finally, clinical benefits of temocillin have been reported in CF patients with *B. cenocepacia* [16,19]. Although, the relationship between sensitivity of isolates and clinical improvement is not clear [19,20]. Indeed, in a study of CF patients concurrently infected with *B. cepacia* complex and *P. aeruginosa*, temocillin was given in combination with an IV aminoglycoside for acute exacerbations of respiratory disease. Clinical improvement was observed in nine out of twelve cases, two of which had pre-treatment isolates which were resistant to temocillin, which suggests that when in-vitro tests show resistance to temocillin there can still be a clinical improvement [19].

2. Methods

2.1. Study design and population

A retrospective cross-over study of patients attending two adult CF centres between 1997 and 2006 was performed. Patients with *B. cepacia* complex or *P. aeruginosa* isolated from sputum were included. Patients included had received a course of antibiotics which included temocillin (TIV) and a further course within ±1 year of the temocillin course which did not include temocillin (NTIV). Courses were excluded if the patient died during the course or if it was their final course before death. Antibiotic prescribing had been based on best physician choice and therefore was influenced by a number of factors including previous antibiotic resistance patterns and allergies/intolerances to other alternative antibiotics. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) at the start and end of each antibiotic course were recorded and expressed as a percentage of the predicted value. The primary endpoint was change in spirometry from baseline and used as a marker of the efficacy of the antimicrobial treatment.

Table 1
Concomitant antibiotics for temocillin and non-temocillin courses

P. aeruginosa ($n=10$)		*B. cenocepacia* ($n=16$)	
Temocillin course[a]	Non-temocillin course	Temocillin course[a]	Non-temocillin course
Tobramycin ($n=9$)	Tobramycin ($n=10$)	Tobramycin ($n=12$)	Tobramycin ($n=13$)
Aztreonam ($n=3$)	Meropenem ($n=3$)	Meropenem ($n=6$)	Meropenem ($n=9$)
Meropenem ($n=1$)	Ceftazidime ($n=4$)	Ceftazidime ($n=2$)	Aztreonam ($n=4$)
Ceftazidime ($n=1$)	Aztreonam ($n=2$)	Chloramphenicol ($n=2$)	Ceftazidime ($n=4$)
Ciproxin ($n=1$)	Tazocin ($n=1$)	Tazocin ($n=2$)	Co-trimoxazole ($n=2$)
Tazocin ($n=1$)	Timentin ($n=1$)	Amikacin ($n=1$)	Chloramphenicol ($n=1$)
Colomycin ($n=1$)	Colistin ($n=1$)		Tazocin ($n=1$)
	Co-trimoxazole ($n=1$)		Vibramycin ($n=1$)

[a] Antibiotics listed were administered in addition to temocillin.

Table 2
Baseline FEV_1 and FVC of whole group and mean (SD) change during temocillin and non-temocillin courses (values expressed as mean±SD)

	Temocillin course		Non-temocillin course	
	Baseline	Increase	Baseline	Increase
FEV_1% predicted	37 (18)	7.12 (11.67)	39 (20)	6.65 (7.62)
FVC% predicted	49 (22)	8.85 (14.04)	53 (23)	7.04 (7.96)

All difference between Temocillin and NON-Temocillin courses and non-statistically significant ($p>0.05$).

2.2. Statistical analysis

Mean and standard deviation were used to describe the characteristics of the patients at baseline of each course. Exploratory data analysis was used to assess the relationship between the change in lung function and baseline lung function. This analysis showed a relationship between baseline lung function and degree of change (i.e. greater changes were associated with higher baseline lung functions). To allow for this paired *t* tests were used to compare the mean change in lung function controlled by baseline between the two IV antibiotic courses.

3. Results

Twenty six patients received temocillin, fourteen were male and twelve female, with a mean (SD) age of 28 (6) years. Fifteen patients were infected with *B. cepacia* complex (*B. cenocepacia*

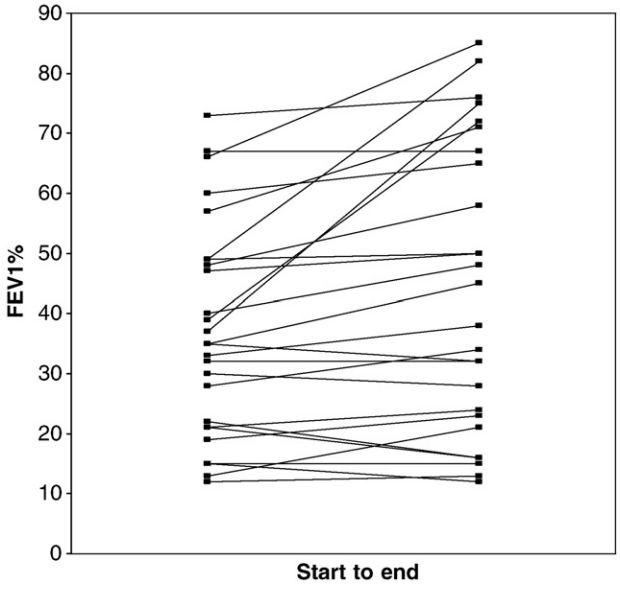

Fig. 1. Change in FEV_1% start to end of temocillin course.

n=14, *B. gladioli* *n*=1) and eleven with *P. aeruginosa*. *Staphylococcus aureus* was also present in three patients (*B. cenocepacia* *n*=1, *P. aeruginosa* *n*=2). Sensitivity of organisms to temocillin was tested in twelve patients; in nine patients the organism was sensitive to temocillin (*B. cenocepacia* *n*=6; *P. aeruginosa* *n*=3) and resistant in three (*B. cenocepacia* *n*=2; *P. aeruginosa* *n*=1). Concomitant antibiotics for temocillin and non-temocillin courses are summarised in Table 1. Baseline lung function was comparable and not significantly different ($p>0.05$) at the beginning of both IV antibiotic courses (Table 2). Duration of infection was 14 days for the non-temocillin course and 21 days for the temocillin course.

Improvement in FEV_1% was similar for the temocillin and non-temocillin courses (Figs. 1 and 2). Analysis of the whole group showed the mean (SD) increase in FEV_1% for the temocillin course was 7.12 (11.67)% and for the non-temocillin course was 6.65 (7.62)%. The mean (SD) of increase in FVC% for the temocillin course was 8.85 (14.04)% and for the non-temocillin course the increase was 7.04 (7.96)% (Table 2).

A mean difference in FEV_1% of 0.46% [95% CI: −4.55 to 5.48%] and a mean difference in FVC% of 1.81% [95% CI: −4.59 to 8.20] were found both in favour of temocillin. When patients were categorized by infecting bacteria and analysed in subgroups there was no statistically significant difference between IV antibiotic courses for either the patients infected with *B. cepacia* complex or with *P. aeruginosa*. In the *B. cepacia* complex group the mean difference in FEV_1% was 1.06% [95%CI: −5.82 to 7.94] and the mean difference in FVC% was 2.13% [95%CI: −6.78 to 11.03], both differences were observed in favour of temocillin. In the patients who isolated *P. aeruginosa* the mean difference in FEV_1% was 0.5% [95%CI: −9.22 to 8.22] and was observed in favour of the non-temocillin course while the mean difference in FVC% was 1.3% [95% CI: −9.55 to 12.15] and observed in favour of the temocillin course (Table 3).

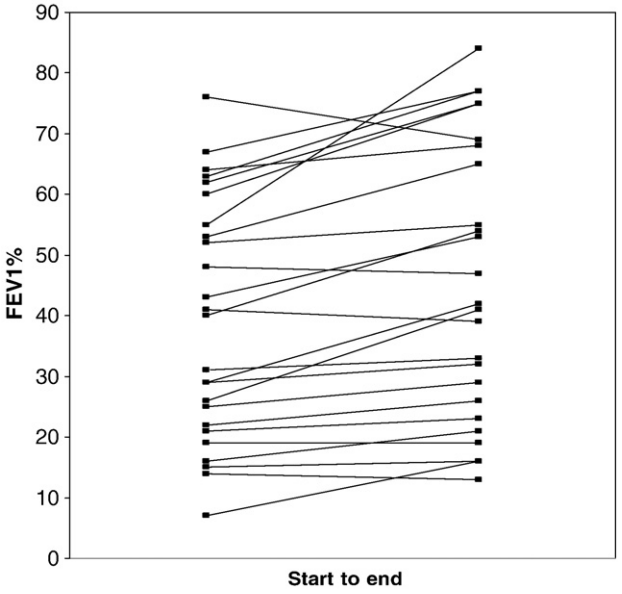

Fig. 2. Change in FEV_1% start to end of non-temocillin course.

Table 3
Mean difference between temocillin and non-temocillin courses (values are expressed as mean difference [95%CI])

	Difference between temocillin and non-temocillin courses	
Group	FEV_1% predicted	FVC% predicted
Whole group	0.46% [−4.55 to 5.48]	1.81% [−4.59 to 8.20]
Bcc group	1.06% [−5.82 to 7.94]	2.13% [−6.78 to 11.03]
Pa group	−0.5% [−9.22 to 8.22]	1.3% [−9.55 to 12.15]

Bcc group: patients infected by *B. cenocepacia*; Pa group: patients infected by *P. aeruginosa*, Whole group: Bcc+Pa.

4. Discussion

In this study temocillin was used primarily for the treatment of severe lung disease as is the practice in both centres. Both IV antibiotic courses elicited improvements in lung function and no significant difference was observed between the temocillin course and the non-temocillin course. The confidence intervals for the differences are wide and may partly be explained by the small sample size.

There are few data available about temocillin and *B. cepacia* complex or *P. aeruginosa* activity. Although, there is evidence to indicate that temocillin alone displays high in-vitro activity against *B. cepacia* complex. Conversely, *P. aeruginosa* is almost always reported resistant although synergistic effects when used in combination with aminoglycoside antibiotics can be seen [8,14,17,18]. Two previous retrospective studies have shown clinical improvement with antibiotic therapy including temocillin for respiratory exacerbations in CF associated with *B. cepacia* complex [16,19]. Clinical improvement occurred in 56% of courses in the study by Lekkas et al. (2006) and 75% of courses in the study by Taylor et al. (1992) compared to 69% in the group colonised with *B. cepacia* complex in the present study [16,19].

This study is the first to compare treatment with temocillin to standard combination therapy, adding to the limited clinical data on the efficacy of temocillin for treating respiratory exacerbations in severe lung disease in CF. These findings need to be investigated in a prospective study however due to the small difference the sample needed would be large. Using data from this study for FEV_1% as the outcome measure, all patients combined, to get a power of 90% to declare equivalence, with an alpha of 5% and an equivalence margin of 5%, 68 patients in each group would be needed.

The retrospective design of this study results in some limitations. Many patients were administered IV antibiotics at home and did not have all outcome measures recorded at the start and end of each course. Moreover, very few patients had CRP, neutrophil count and weight recorded preventing any further analyses. The longer duration of the temocillin course indicates that at this stage patients were sicker and despite this there was no difference in treatment effects between courses. Finally, as temocillin was given in conjunction with an aminoglycoside it is impossible to assess the individual effects

of each antibiotic. However, aminoglycosides have been administered to all patients in both courses which decreases in part the influence of this second antimicrobial, and allows for comparison between temocillin and the other treatment, as each patient becomes their own control.

In conclusion these results support previous reports that the efficacy of temocillin is equivalent for *B. cepacia* complex when compared to standard combination therapy for an acute exacerbation of respiratory disease due to multi-resistant bacteria in CF [16,19].

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References

[1] Rodriguez-Villalobos H, Malavoille V, Frankard J, de Mendonca R, Nonhoff C, Struelens MJ. In vitro activity of temocillin against extended spectrum beta-lactamase-producing *Escherichia coli*. J Antimicrob Chemother 2006;57(4):771–4.

[2] Edmondson RA, Reading C. Beta-lactamase stability of temocillin. Drugs 1985;29(suppl 5):64–6.

[3] Stapleton P, Shannon K, Phillips I. The ability of beta-lactam antibiotics to select mutants with depressed beta-lactamase synthesis from *Citobacter freundii*. J Antimicrob Chemother 1995;36(3):483–96.

[4] Chen HY, Williams JD. The Activity of temocillin against *Enerobacteriaceae, Pseudomonas* and *Haemophilus influenzae*. Drugs 1985;29 (Suppl 5):85–90.

[5] Guiliani F, Docquier JD, Riccio ML, Pagani L, Rossolini GM. OXA-46, a new class D β-lactamase of narrow substrate specificity encoded by a bla_{VIM-1}-containing integron from a *Pseudomonas aeruginosa* clinical isolate. Antimicrob Agents Chemother 2005;49(5):1973–80.

[6] Bauernfeind A. Bacteriostatic and bactericidal activity of penicillins at constant and variable concentrations. Drugs 1985;29(Suppl 5):9–14.

[7] Martinez-Beltran J, Loza E, Gomez-Alferez A, Romero-Vivas J, Bouza E. Temocillin: in-vitro activity compared to other antibiotics. Drugs 1985;29 (Suppl 5):91–7.

[8] Jules K, Neu HC. Antibacterial activity and beta-lactamase stability of temocillin. Antimicrob Agents Chemother 1982;22(3):453–60.

[9] Verbist L, Verhaegen J. Effect of temocillin in combination with other beta-lactam antibiotics. Antimicrob Agents Chemother 1984;25(1):142–4.

[10] Bolivar R, Weaver SS, Bodey GP. Comparative in vitro study of temocillin (BRL 17421), a new penicillin. Antimicrob Agents Chemother 1982;21(4):641–5.

[11] Boon RJ, Beale AS. Studies with temocillin in the hamster model of antibiotic-associated colitis. Drugs 1985;29(Suppl 5):57–63.

[12] Tanphaichitra D, Kanjanapanjapol S, Srimuang S, Robinson O. Use of temocillin in typhoid fever, hepatobiliary disease and other infections. Drugs 1985;29(Suppl 5):201–5.

[13] Legge JS, Reid TM, Palmer JB. Clinical efficacy, tolerance and pharmacokinetics of temocillin in patients with respiratory tract infections. Drugs 1985;29(Suppl 5):118–21.

[14] Verbist L. In vitro activity of temocillin (BRL 17421), a novel beta-lactamase-stable penicillin. Antimicrob Agents Chemother 1982;22(1):157–61.

[15] Williams JD, Chen HY. The place of temocillin in the treatment of hospital infections. Drugs 1985;29(Suppl 5):234–9.

[16] Lekkas A, Gyi KM, Hodson ME. Temocillin in the treatment of *Burkholderia cepacia* infection in cystic fibrosis. J Cyst Fibros 2006;5:121–4.

[17] Slocombe B, Cooper CE, Griffen KE, White AR. Temocillin. In vitro antibacterial activity. Drugs 1985;29(Suppl 5):49–56.

[18] Bonacorsi S, Fitoussi F, Lhopital S, Bingen E. Comparative in vitro activities of meropenem, imipenem, temocillin, piperacillin, and ceftazidime in combination with tobramycin, rifampin, or ciprofloxacin against *Burkholderia cepacia* isolates from patients with cystic fibrosis. Antimicrob Agents Chemother 1999;43(2):213–7.

[19] Taylor RF, Gaya H, Hodson ME. Temocillin and cystic fibrosis: outcome of intravenous administration in patients infected with *Pseudomonas cepacia*. J Antimicrob Chemother 1992;29(3):341–4.

[20] Gray JM, Leiper JM, Lawson DH, Cowan W, Baird A, Sleigh JD. Temocillin in the treatment of chest infections. Drugs 1985;29(Suppl 5):197–200.