A brief review of moxifloxacin in the treatment of elderly patients with community-acquired pneumonia (CAP)

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Abstract: Community-acquired pneumonia (CAP) remains a common cause of morbidity and a potentially life-threatening illness throughout the world mainly in elderly patients. Initial antibacterial treatment, usually empirical, should be as effective as possible in order to assure rapid clinical resolution and reduce high rates of hospitalization and mortality especially affecting aged patients. New fluoroquinolones with potent activity against the most important respiratory pathogens including *Streptococcus pneumoniae*, a key pathogen mainly in old patients with CAP, have been recently suggested by several international guidelines as monotherapy for the treatment of most CAP patient categories. Among newer derivatives, moxifloxacin, an advanced generation 8-methoxy quinolone, has demonstrated good clinical and bacteriological efficacy in large, well designed clinical trials both in adults and old patients with CAP, achieving also in aged people efficacy comparable with that of standard treatments. Good pharmacokinetic characteristics such as excellent penetration into respiratory tract tissues and fluids, optimal bioavailability, simplicity of once-daily dosing, and good tolerability, represent potential advantages of moxifloxacin over other therapies. In addition, primarily due to a shorter length of hospital stay, moxifloxacin has been shown to save costs compared with standard therapy.

Keywords: moxifloxacin, community-acquired pneumonia, elderly patients

Introduction

Pneumonia more frequently afflicts patients aged ≥65 years, with an incidence that increases proportionally with increasing age. It was estimated that ~ 1 in 20 persons aged ≥85 years experiences a new community-acquired pneumonia (CAP) episode each year. Several factors such as comorbidities, nutritional status, cognitive impairment may contribute to the frailty and the increased susceptibility of these patients to pneumonia. Additionally, hospitalization, required in approximately 40% of episodes among elderly persons, is associated with a high risk of readmission within the following year and with high mortality rates (40%) (Janssens 2005; Schmidt-Ioanas and Lode 2006).

Appropriate and timely antibiotic treatment is required for elderly patients in order to enhance the likelihood of a good clinical outcome. Patients requiring hospital admission for treatment of CAP should be promptly treated with potent broad spectrum intravenous antimicrobials in order to cover the major respiratory pathogens involved. Beta-lactam antibiotics have been commonly prescribed over the past decades for the treatment of outpatients and patients hospitalized with CAP; however, the emergence in recent years in several countries in the world of penicillin-resistant *Streptococcus pneumoniae* isolates (resistance rates ranging from less than 5% to over 50%) has forced a reassessment of the approach to treating CAP (Heffelfinger et al 2000).

In this context, recent fluoroquinolones with antipneumococcal activity have been suggested as monotherapy in several international guidelines for the management of

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both outpatients and inpatients on a general medical ward and as a part of combination therapy for intensive care patients (BTS 2001; Niederman et al 2001; Mandell et al 2003). Among the newest generation of fluoroquinolones, moxifloxacin has been shown to display excellent activity against the most important respiratory pathogens including multi-drug resistant pneumococcal strains, and to possess satisfactory pharmacokinetic and pharmacodynamic characteristics at respiratory level (Balfour et al 2000; Zhanel et al 2002). This review will focus on the efficacy of moxifloxacin in the treatment of elderly patients with CAP and on the safety and tolerability aspects of the drug in this population.

CAP in the elderly

Pneumonia represents the leading infection-related cause of death and the fifth cause of overall mortality in the geriatric population (Schmidt-Ioanas and Lode 2006). Several factors such as alcoholism, asthma, immunosuppression, lung and heart diseases, institutionalization, and increasing age have been found to be associated with an increased risk of pneumonia in the elderly. The clinical presentation of CAP in elderly patients is frequently characterized by a reduced prevalence of nonrespiratory symptoms and by the absence of the typical acute symptoms observed in young adults (Torres et al 1999; Loeb 2003; Niederman and Ahmed 2003; Schmidt-Ioanas and Lode 2006). Elderly people sometimes show only atypical clinical manifestations (eg, weakness, urinary incontinence, and changes in mental status). These atypical findings could be responsible for a delay in diagnosis and treatment contributing to increased morbidity and mortality.

The term CAP should be reserved, in the elderly population, for pneumonia acquired outside the nursing home setting, since nursing home-acquired pneumonia (NHAP) differs from CAP in terms of its etiology and clinical manifestations (Lieberman and Lieberman 2000).

Although in most of the elderly the etiological agent of CAP remains undetermined because of the difficulty in attaining adequate bronchial specimens and/or contamination of sputum by oral colonizing Gram-negative bacilli, *S. pneumoniae* represents the most frequently isolated pathogen in this population, accounting for up to 50% of the causative agents (Marrie 2000; Niederman et al 2001). Moreover, increasing age, per se, represents a risk factor for drug-resistant *S. pneumoniae.* Relatively high frequency is also reported in the elderly population for *Haemophilus influenzae* and *Moraxella catarrhalis*, while *Staphylococcus aureus* and Gram-negative bacteria occur less frequently in

post-viral influenza and in high-risk patient groups, respectively (Cunha 2001). Atypical pathogens, mainly *Chlamydia pneumoniae*, have been emphasized recently in old people as the cause of CAP and NHAP outbreaks with a high mortality rate in nursing homes. Outbreaks of pneumonia owing to respiratory viruses (influenza and respiratory syncytial viruses) may also occur in this population. Etiology of aspiration pneumonia, which represents 5%–15% of CAP in elderly patients, in outpatients is associated with *S. aureus*, *S. pneumoniae*, and *H. influenzae*, while in hospitalized or nursing home residents more likely results in infection by Gram-negative rods. In addition, anerobes may also contribute to the pathogenesis of aspiration pneumonia, although evidence for their major role has not been confirmed in recent studies (Schmidt-Ioanas and Lode 2006).

Despite advances in diagnosis and therapy, the management of pneumonia still represents a challenge to the physicians mainly in old patients. When respiratory infections occur, rapid diagnosis and prompt administration of appropriate antibacterial therapy that ensures adequate coverage of the major pathogens causing CAP in old people is likely to increase the probability of a successful outcome, reducing the risk of hospitalization and death and preventing the spread of antimicrobial resistance (Rajagopalan and Yoshikawa 2001; Neralla and Meyer 2004).

The initial antibiotic therapy for elderly patients with CAP should be empirical and the selection of antibacterials should be based upon local resistance patterns of chosen drugs. The algorithm for therapy suggested by international guidelines recommends the use of either a selected beta-lactam combined with a macrolide or monotherapy with a new antipneumococcal quinolone for both adult outpatients and inpatients (not in an intensive care unit) (Niederman et al 2001; BTS guidelines 2001; Mandell et al 2003). No difference in antimicrobial selection for elderly with CAP has been suggested by the recent Infectious Diseases Society of America update containing a new chapter on pneumonia in the elderly (Mandell et al 2003).

Moxifloxacin: a "respiratory quinolone"

Moxifloxacin, like other recent fluoroquinolones, has a broad antibacterial spectrum that provides excellent coverage of the major respiratory tract pathogens. It displays excellent activity against Gram-negative bacilli (Enterobacteriaceae, *H. influenzae*, *M. catarrhalis*) and improved Gram-positive activity against *S. pneumoniae* (both penicillin-susceptible and penicillin-resistant strains), and *S. aureus* compared

with ciprofloxacin. Moreover, it retains good activity against atypical pathogens with a significantly better antibacterial effect against *Legionella pneumophila* compared with erythromycin, and displays improved activity against anerobes compared with ciprofloxacin (Zhanel et al 2002; Tano et al 2005).

Moxifloxacin may inhibit both DNA gyrase and Topoisomeras IV, but its mechanism of action is slightly different from that of other fluoroquinolones. For *S. pneumoniae* the preferential target of fluoroquinolone action appears to vary depending on the chosen antibacterial agent. Moxifloxacin primarily targets the gyrA subunit of DNA gyrase, whereas levofloxacin and other less recent derivatives such as ofloxacin and ciprofloxacin preferentially target the subunits parC or parE of the topoisomerase IV. Owing to this difference, moxifloxacin may retain high activity against increasingly common pneumococcal strains bearing substitutions in topoisomerase IV due to the wide use of old derivatives. In addition, due to modification of the substituent at the C-7 position of the fluoroquinolone structure, moxifloxacin is a poor substrate for active efflux in *S. pneumoniae* (Pestova et al 2000).

Moxifloxacin may be administered as oral and/or intravenous formulations with excellent bioavailability; the drug is well absorbed after oral administration and achieves good tissue penetration at respiratory level, reaching higher concentrations in alveolar macrophages (56.7 µg/mL) and epithelial lining fluid (20.7 µg/mL) than in serum (3.2 µg/mL) after a single 400 mg oral dose (Soman et al 1999). Recently, high intrapulmonary concentrations have also been confirmed in older adults (Capitano et al 2004). Moreover, moxifloxacin both intravenously and orally exhibts high penetration in lung tissue with maximal lung concentrations of 12.37 µg/g and 16.21 µg/g for iv and oral administration respectively (Breilh et al 2003).

The pharmacokinetic behaviour of moxifloxacin is not significantly altered by the aging processes. This is consistent with moxifloxacin being metabolized mainly by means of phase II hepatic reactions, the activity of which was shown not to decline with age (Pea et al 2006). Dose adjustment does not appear to be necessary in patients of advanced age or those with mild to moderate renal or hepatic impairment (Balfour and Lamb 2000; Ball et al 2004**)**. The safety profile of moxifloxacin is in line with established fluoroquinolones. Reactions of the gastrointestinal tract are the most often observed adverse effects during therapy. Like other fluoroquinolones, moxifloxacin can cause QT interval prolongation; therefore it should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hy-

pokalemia or hypomagnesemia, and patients receiving class IA (eg, quinidine, procainamide) or class III (eg, amiodarone, sotalol) antiarrhytmic agents or other drugs such as certain antimicrobials (eg, erythromycin, halofantrine, pentamidine), certain antihistaminics (eg, astemizole, mizolastine, terfenadine), neuroleptics, and tricyclic antidepressive agents (Stahlmann and Lode 2003; Miravitlles 2005). Moxifloxacin has a low propensity for causing phototoxic reactions and a low potential for causing excitatory effects and, like other agents of the group, can potentially cause tendon disorders mainly in aged patients in presence of concomitant use of corticosteroids and chronic renal diseases (Balfour and Lamb 2000; Zhanel et al 2002; Stahlmann and Lode 2003). Moxifloxacin lacks other significant drug interactions with a number of commonly prescribed drugs, although its absorption is decreased by concomitant administration of iron and cationic antacids (Ball et al 2004).

Clinical efficacy of moxifloxacin in CAP

Clinical efficacy of moxifloxacin in CAP has been compared in some trials with different comparator agents both in adult and old patients (Table 1). All studies excluding those of Patel et al (2000), and Fogarty et al (2005) are comparative trials of moxifloxacin versus standard therapies including beta-lactams (amoxicillin, amoxicillin-clavulanate, ceftriaxone) alone or in combination with a macrolide (erythromycin, roxithromycin, clarithromycin), a macrolide alone (clarithromycin), or another fluoroquinolone, levofloxacin (Fogarty et al 1999; Hoeffken et al 2001; Petitpretz 2001; Finch et al 2002; Torres et al 2003; Jardim et al 2003; Katz et al 2004; Portier et al 2005; Welte et al 2006; Anzueto et al 2006). All these trials have confirmed that moxifloxacin is at least as effective as comparator regimens, since the overall clinical and bacteriological success rates for moxifloxacin (range, 83%–97% and 77%–97%, respectively) are comparable to those obtained for comparators (range, 80%–95% and 62%–93%, respectively). Aged subjects as a proportion of total number of patients included in these studies are not always available; clinical trials providing such demographic data (Petitpretz et al 2001; Torres et al 2003; Jardim et al 2003; Portier et al 2005; Welte et al 2005), and the only study entirely carried out on a population of elderly patients (Anzueto et al 2006) will be briefly summarized.

Welte et al (2005) compared the efficacy, safety, and speed and quality of defervescence of sequential intravenous or oral moxifloxacin (400 mg od) and high dose ceftriaxone (2 g intravenously od) with or without erythromycin (1 g

Table 1 Summary of main recent clinical trials with moxifloxacin in adult and old patients with community acquired-pneumonia

Authors	Study design	No. of patients PPP	Treatment	Test of cure (TOC)	Clinical success in PPP (%)	Bacteriological success[a] No. of patients (%)	Age mean values ± SD(range)	PSI class[b]
Fogarty 1999	Randomized double-blind	382	10 days MXF po 400 mg od (n = 194); 10 days CLA po 500 mg bid (n = 188)	End of therapy	97.0; 95.0	99 (97.0); 100 (93.0)	48; 49	NA
Patel 2000	Open-label non comparative	196	10 days MXF po 400 mg od	0–6 days post therapy	94.0	106 (91.0)	49 (18–85)	NA
Hoeffken 2001	Randomized double-blind	531	10 days MXF po 200 mg od (n = 180); 10 days MXF po 400 mg od (n = 177); 10 days CLA po 500 mg bid (n = 174)	3–5 days post therapy	93.9; 94.4; 94.3	29 (72.5); 37 (78.7); 29 (70.7)	48.4 ± 20.6; 48.0 ± 20.8; 48.2 ± 19.2	NA
Petitpretz 2001	Randomized double-blind	362	10 days MXF po 400 mg od (n = 177); 10 days AMX po 1000 mg tid (n = 185)	3–5 days post therapy	91.5; 89.7	61 (89.7); 56 (82.4)	52.0 ± 20.5 (≥70:25%); 49.9 ± 20.6 (≥70:22%)	NA
Finch 2002	Randomized open-label	538	7–14 days MXF iv/po 400 mg od (n = 258); 7–14 days AMX-CLAV iv(1200 mg tid)/po (625 mg tid) ± CLA iv/po (500 mg bid) (n = 280)	5–7 days post therapy	93.4; 85.4	60 (93.7); 58 (81.7)	55.2 ± 20.6; 55.9 ± 19.6	NA
Torres 2003	Randomized double-blind	446	Up to 14 days MXF po 400 mg od (n = 215); Up to 14 days AMX (1000 mg tid) or CLA (500 mg bid) alone or in combination (n = 231)	7–10 days post therapy	93.5; 93.9	NA; NA	52.7 ± 18.7 (≥70:22%); 49.3 ± 18.7 (≥70:18%)	I–III 80.6% IV 17.6% V 1.7%; I–III 84.9% IV 13.9% V 1.2%
Jardim 2003	Randomized double-blind CAP with S. pneumoniae infection	70	10 days MXF po 400 mg od (n = 34); 10 days AMX 500 mg tid (n = 36)	3–5 days post therapy	94.1; 91.7	15 (88.2); 14 (87.5)	51.9 (>65:28.2%); 48.6 (>65:31.1%)	NA

(Continued)

Table 1 Continued

Authors	Study design	No. of patients PPP	Treatment	Test of cure (TOC)	Clinical success in PPP (%)	Bacteriological success[a] No. of patients (%)	Age mean values ± SD(range)	PSI class[b]	
Katz 2004	Randomized open-label	221	7–10 days MXF iv/po 400 mg od (n = 108)	7–14 days post therapy	83.3	14 (82.3)	59.4 ± 19 (18–93)	I–III	75.0%
								IV	20.0%
								V	5.0%
			7–10 days CRO (2000 mg iv qd) → FUR (500 mg po bid) ± AZM ± MTZ (n = 113)		79.6	15 (62.5)	58.7 ± 20.5 (18–94)	I–III	77.0%
								IV	18.0%
								V	5.0%
Portier 2005	Randomized open-label	289	10 days MXF po 400 mg od (n = 151)	5–7 days post therapy	86.8	23 (76.7)	59.3±17.9 (>65: 46.8%)	NA	
			10 days AMX-CLAV (1000/125 mg tid) + ROX (150 mg bid) (n = 138)		87.0	23 (74.2) (>65: 53.1%)	62.4±18		
Fogarty 2005	Pooled data from 6 non-comparative trials (S.pneumoniae CAP)	131	7–14 days MXF po or iv/po 400 mg od	7–35 days post therapy	95.4	104 (92.9)	56.4 (20–88)	NA	
Welte 2005	Randomized open-label	317	7–14 days MXF iv/po 400 mg od (n = 161)	5–20 days post therapy	85.7	NA	(≥65: 43.5%)	I–III	83.2%
								IV	16.1%
								V	0.6%
			7–14 days CRO (2000 mg od) ± ERY(1000 mg iv tid) (n = 156)		86.5	NA	(≥65: 41.0%)	I–III	82.7%
								IV	16.7%
								V	0.6%
Anzueto 2006	Randomized double-blind	281	7–14 days MXF iv/po 400 mg od (n = 141)	5–21 days post therapy	92.9	17 (81.0)	77.9±7.1 (65–95) (>75: 64.5%)	I–III	48.2%
								IV	29.1%
								V	7.1%
									13.5% [c]
			7–14 days LEV iv/po 500 mg od (n = 140)		87.9	21 (75.0)	77.4±7.7 (65–98) (>75: 57.1%)	I–III	40.7%
								IV	36.4%
								V	4.3%
									18.6% [c]

[a]eradication/presumed eradication in microbiologically valid population.
[b]PSI, pneumonia severity index score (Fine et al 1997).
[c]severe ATS CAP severity score according to guidelines of the American Thoracic Society (Niederman et al 2001).
Abbreviations: AMX, amoxicillin; AMX-CLA, amoxicillin-clavulanate; AZM, azithromycin; CLA, clarithromycin; CRO, cefriaxone; ERY, erithromycin; FUR, cefuroxime; LEV, levofloxacin; MTZ, metronidazole; MXF, moxifloxacin; n, number of patients; PPP, per-protocol population; ROX, roxithromycin.

intravenously every 6–8 hours) for 7–14 days in patient with CAP requiring parenteral therapy. In both arms of the study the validated per-protocol (PP) population aged ≥65 years achieved rates of 43.5% for moxifloxacin and 41.0% for comparators respectively. Clinical response rates at the test of cure (TOC) visit in the validated PP population (317 patients) were 85.7% in the moxifloxacin group (138 of 161 patients) and 86.5% in the ceftriaxone ± erythromycin group (135 of 156 patients); at the end of treatment, resolution was reported for 87.6% and 88.5% of patients for moxifloxacin and for the other group respectively. In subgroups of patients matched for age, sex, and pneumonia severity index score, no significant differences were observed at the TOC visit in both treatment groups. Compared with the ceftriaxone ± erythromycin, the moxifloxacin regimen was observed to shorten the duration of hospitalization by a mean of 1.3 days in the validated PP population. In addition, defervescence and relief of signs and symptoms associated with CAP such as chest pain and weakness, occurred significantly earlier in the moxifloxacin-treated group than in the comparator-treated group. No relevant differences between treatment groups in the incidence for drug-related adverse events were observed and the vast majority of them were mild to moderate.

In a recent multicenter randomized open-label study, Portier et al (2005) compared 10 days oral treatment with moxifloxacin (400 mg od) with amoxicillin–clavulanate (1000/125 mg tid) plus roxithromycin (150 mg bid) for non-severe CAP in adults with risk factors. Patients aged >65 years included in the intention-to-treat (ITT) analysis were 46.8% (80/171) and 53.1% (93/175), respectively, and half of the entire population had at least one comorbid condition. Respective per-protocol clinical success rates at the TOC visit for moxifloxacin and comparator were 131 of 151 (86.8%) and 120 of 138 (87.0%), with a 95% confidence interval (CI) of –8.0 to 7.6 for the difference. Similar success rates were reached and maintained for patients with bacteriologically proven CAP and for those in whom the causative pathogen was *S. pneumoniae*. The bacteriological success rates at the TOC visit were also comparable for moxifloxacin- and comparator-treated patients with respective success rates of 23 of 30 (76.7%) and 23 of 31 (74.2%). Persistent clinical success rates at follow-up were 118 of 120 (98.3%) and 102 of 106 (96.2%) with a 95% CI of –2.2 to 6.4 for the difference. The clinical success rates were also maintained when subgroups were analyzed according to risk factors such as age (>65 years), comorbidities, prior hospitalization, and alcohol consumption. The numbers of drug-related adverse events (predominantly digestive disorders) in the ITT

population were comparable for both treatment arms: 24.6% (42 patients) for moxifloxacin and 28.6% (50 patients) for comparator group.

Age ≥70 years was reported for 22% of moxifloxacin-treated patients (52/233) and for 18% of comparator-treated patients (44/244) of the ITT population, in the study of Torres et al (2003). In this study, 564 patients were randomized to either oral moxifloxacin (400 mg od) or to standard oral therapy (amoxicillin 1 g tid or clarithromycin 500 mg bid alone or in combination) for up to 14 days using a double-blind procedure. In the PP population (446 patients), clinical success was reported for 201 of 215 (93.5%) and 217 of 231 (93.9%) in the moxifloxacin and standard groups, respectively, at 7–10 days post-therapy. At 28–35 days follow-up, continued clinical cure was observed in 183 of 192 (95.3%) moxifloxacin and 207 of 221 (93.7%) standard groups. Moxifloxacin treatment was significantly better tolerated than standard regimens with fewer adverse events and premature discontinuation. Drug-related adverse events were reported in 55 of 274 (20%) moxifloxacin and 86 of 279 (31%) standard patients with a predominance of mild gastrointestinal upsets.

The study of Jardim et al (2003) evaluated the efficacy and safety of treatment with either moxifloxacin or amoxicillin administered for 10 days to patients suspected of having CAP caused by a pneumococcal infection. Over a total of 84 patients (ITT population) included in the study and enrolled from 5 Latin American countries, 70 patients (PP population, 34 patients for moxifloxacin and 36 for amoxicillin) were evaluated at the end of the trial. In the ITT population patients aged >65 years comprised 28.2% (11/39) and 31.1% (14/45) of the moxifloxacin and amoxicillin arm, respectively. The clinical success rate in the PP population at the final visit after treatment was 94.1% (32/34) for moxifloxacin and 91.7% (33/36) for amoxicillin, while the bacteriological success rate in microbiologically valid patients was 88.2% (15/17) and 87.5% (14/16), respectively. In terms of pneumococcal etiology 15 of 34 and 13 of 36 patients evaluated and treated with moxifloxacin and amoxicillin, respectively, had proven pneumococcal pneumonia with prevalence of isolates with reduced susceptibility to penicillin. Drug-related adverse events in both treatment groups were mainly mild to moderate in intensity and were subsequently resolved.

Petitpretz et al (2001) compared the efficacy and safety of moxifloxacin with amoxicillin for the treatment of mild-to-moderate, suspected pneumococcal CAP in adult patients; 25% and 22% respectively of the PP population (362 patients) were aged ≥70 years. Clinical success rate at the TOC visit

in the PP population was 91.5% for moxifloxacin and 89.7% for amoxicillin, while the clinical cure rate in patients with proven pneumococcal pneumonia was similar in both treatment groups (87.8%). The bacteriological success rate in 136 bacteriologically evaluable patients at the TOC visit was 89.7% for moxifloxacin and 82.4% for amoxicillin. The bacteriological success rate against *S. pneumoniae* was 89.6% for moxifloxacin and 84.8% for amoxicillin. The frequency of adverse events was comparable in both treatment groups.

Finally, the study of Anzueto et al (2006) was the first comparative trial entirely carried out in hospitalized elderly patients (mean age 77.4 ± 7.7 years). In this double-blind, randomized trial, eligible patients for clinical efficacy were stratified by CAP severity to receive treatment with either intravenous/oral moxifloxacin (400 mg od) or intravenous/oral levofloxacin (500 mg od) for 7–14 days. Cure rates at the TOC visit for the clinically valid (PP) population (141 and 140 patients in the moxifloxacin and levofloxacin group, respectively) were 92.9% in the moxifloxacin arm and 87.9% in the levofloxacin arm (95% CI, –1.9 to 11.9; p = 0.2). Moreover, in subgroup analyses based on CAP severity and patient age, clinical cure rates in the moxifloxacin arm were consistently higher than, although not statistically significantly different from, those for levofloxacin. In the moxifloxacin group, cure rates were 92.6% for patients with mild or moderate CAP and 94.7% for patients with severe CAP, compared with cure rates of 88.6% and 84.6%, respectively, in the levofloxacin group. Cure rates in the moxifloxacin arm were 90% for patients aged 65–74 years and 94.5% for patients aged ≥75 years, compared with 85.0% and 90.0%, respectively, in the levofloxacin arm. Bacteriological success at the TOC visit in the microbiologically valid population was 81.0% in the moxifloxacin arm (17 of 21 patients) and 75.0% in the levofloxacin arm (21 of 28 patients) (p = 0.9). The bacteriological response was in agreement with the clinical response: clinical cure rates for the microbiologically valid population were 81.0% in the moxifloxacin arm (17 of 21 patients) vs 76.7% in the levofloxacin arm (23 of 30 patients) (95% CI, –0.22 to 0.31; p = 0.98).

Although no differences emerged in duration of stay or duration of intravenous therapy between the two regimens, sequential intravenous/oral moxifloxacin therapy provided significantly higher clinical recovery rates by day 3–5 after initiation of treatment. No statistically significant differences were observed between the treatment groups in drug-related adverse events.

Safety considerations

Aging is well known to be associated with physiological changes and a higher risk of drug interactions; for these reasons special attention needs to be directed towards the safety of medications in elderly people. Cumulative safety data from the most recent clinical trials and post-marketing surveillance studies including a large number of patients have shown that gastrointestinal complaints such as nausea, diarrhea, and dizziness were the most commonly reported drug-related adverse events (7.1, 5.2, and 2.6%, respectively) following administration of an oral dosage of 400 mg od (Ball et al 2004). Gastrointestinal and central nervous system (CNS) disturbances are in line with those of other fluoroquinolones; however, as adverse CNS reactions are of particular concern for the elderly, old patients with impairments of the CNS (eg, epilepsy, pronounced arteriosclerosis) should be treated with a quinolone only under close supervision (Stahlmann and Lode 2003).

The safety of oral moxifloxacin in adult and elderly patients pooled by age group (4939 patients aged <65 years, 842 patients aged 65–74 years, 489 patients aged ≥75 years) has been evaluated in a retrospective analysis versus comparator (cefuroxime and clarithromycin, the most frequently used comparators) (Andriole et al 2005). Drug-related adverse event rates associated with oral moxifloxacin or the comparator therapy used in these studies showed no significant increase with advancing age. No arrhythmias related to corrected QT interval prolongation were reported in this large group of young and elderly patients and a similar number of deaths was observed between the treatment groups (17 moxifloxacin, 19 comparator). The cardiac rhythm safety of moxifloxacin versus levofloxacin in high-risk elderly patients with CAP (eg, comorbid conditions and multiple medications) was recently evaluated in a randomized, double-blind trial (Morganroth et al 2005). In the studied population (394 patients; two-third of the patients were >75 years old, and 74.1% had a history of cardiac disease), iv/oral moxifloxacin demonstrated a comparable cardiac rhythm safety profile to iv/oral levofloxacin; moreover, no deaths clearly related to study drugs were reported to occur during the observation period.

To date, sporadic moxifloxacin-related adverse events observed in the elderly population may be limited to very few cases: these include tendinitis, in a 65-year-old female (Burkhardt et al 2004), nephrotoxicity in a 68-year-old woman who experienced acute tubulointerstitial nephritis developed approximately 10 days after the end of moxifloxacin therapy for a non-specific bronchial infection (Argirov et al 2005), and cholestasis in a 69-year-old man treated with moxifloxacin because of a respiratory infection (Soto et al 2002). Of major concern, several case reports have recently

documented, mainly in old patients, a clinically relevant interaction between moxifloxacin and warfarin with significantly elevated international normalized ratio (INR) in patients receiving concomitant therapy (Arnold et al 2005; Elbe and Chang 2005). Routine, frequent INR monitoring and a suitable warfarin dosage adjustment should be recommended mainly in old patients receiving this combination of drugs.

Conclusion

Pneumonia in the elderly is a serious illness that requires rapid management. The treatment of CAP is often based on an empirical approach; therefore, antibiotic choice must cover key pathogens and take into account, at the same time, the steady increase in resistance observed worldwide during recent years in important respiratory pathogens. Basically, the antibiotic therapy of CAP in the elderly should mainly cover *S. pneumoniae*, including the penicillin-resistant strains in countries with a high prevalence; when previous antimicrobial treatment, prior hospitalization, or structural lung disease are present, *Pseudomonas aeruginosa* should be suspected and should guide the antibiotic choice; and enteric Gram-negative rods and anerobes should be considered in residents of nursing homes and in suspicion of aspiration pneumonia. Isolates of penicillin- or macrolide-resistant pneumococci are now a consideration in elderly patients, as an age of >65 years represents a recognized risk factor for infection with these organisms. Given the increasing resistance of *S. pneumoniae* to the traditional first-line agents employed in CAP treatment, recent fluoroquinolones with improved antipneumococcal activity are emerging as important therapeutic options. Moxifloxacin, thanks to its excellent microbiological, pharmacokinetic, and pharmacodynamic profile, fulfils all the requirements of an optimal antimicrobial agent useful for lower respiratory tract infections. Results of clinical trials available so far have shown that generally moxifloxacin may achieve more than 90% cure in all patients irrespective of severity of pneumonia, patient's age, and underlying comorbidities, and may retain bacteriological and clinical efficacy also in presence of penicillin-, macrolide- and multidrug-resistant pneumococcal isolates (Petitpretz et al 2001; Finch et al 2002; Jardim et al 2003; Fogarty et al 2005). In addition, moxifloxacin therapy has been observed to be often associated with faster clinical recovery than comparator therapies.

Finally, based on pharmacoeconomic considerations, the option of moxifloxacin sequential therapy, leading to early discharge from the hospital, may save costs compared with standard therapy (Drummond et al 2003).

Proven clinical and bacteriological efficacy and safety profile in line with established fluoroquinolones and comparator agents suggest that moxifloxacin should prove a successful agent for the treatment of elderly patients with CAP. The growing use of the new-generation fluoroquinolones could, however, lead to emergence of resistant pneumococcal isolates; although resistance is currently low, levofloxacin clinical failures in the management of pneumococcal pneumonia have been reported recently, requiring a re-evaluation of the newer agents (Ferrara 2005). No reports have shown the same phenomenon in patients treated with the more active moxifloxacin, suggesting that the selection of the most potent fluoroquinolone, which may assure the best coverage against *S. pneumoniae,* will reduce the opportunity for resistance to develop. However, to preserve the activity of moxifloxacin for the future, it seems prudent to avoid the massive use of this new agent as long as effective standard antibiotics for the treatment of CAP are still available.

Targeted and judicious use of newer fluoroquinolones in selected CAP patients, including those with infection owing to highly-resistant pneumococci, or following treatment failure with first-line regimen, will minimize the emergence of bacterial resistance to the entire class and maintain class efficacy (Heffelfnger et al 2000).

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