Clinical Efficacy of Moxifloxacin in the Treatment of Exacerbations of Chronic Bronchitis: A Systematic Review and Meta-Analysis

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OBJECTIVE: As the research undertaken to date on the efficacy of the new antibiotics in the treatment of exacerbations of chronic bronchitis has taken the form of trials designed to demonstrate equivalence, we have no data on the advantages associated with the use of these new drugs with greater bactericidal activity. Our objective was to compare the clinical efficacy of moxifloxacin to that of the antibiotic regimens routinely used to treat such exacerbations by a systematic review of the literature and a meta-analysis.

METHODS: A manual and electronic search was performed to identify all clinical trials carried out between January 1997 and July 2005 to compare moxifloxacin and the antibiotics that are currently the first line treatment for exacerbations of chronic bronchitis. Once it had been established that the designs of the trials included were acceptable, a meta-analysis of clinical outcomes was performed.

RESULTS: Of the 45 studies identified, 9 met the inclusion criteria. Of these, 5 were double-blind randomized trials and 4 were randomized open trials. The 9 trials comprised a total of 3,905 patients. The aggregate standardized mean difference in clinical success rate was 1.5% (95% confidence interval, –0.4% to 3.4%). Bacterial eradication rates ranged from 68.4% to 96% for the standard regimens, and from 87.7% to 96% for moxifloxacin. No intergroup differences in the percentages of patients lost to follow-up were observed in any of the studies.

CONCLUSIONS: Although the trials reviewed were designed to demonstrate equivalence, meta-analysis revealed that the clinical success rate achieved with moxifloxacin tended to be higher than that obtained in the groups that received standard antibiotic treatment.

Key words: Moxifloxacin. Exacerbations. Chronic bronchitis. Antibiotics. Meta-analysis.

Eficacia clínica del moxifloxacino en el tratamiento de las agudizaciones de la bronquitis crónica. Revisión sistemática y metaanálisis

OBJETIVO: Debido a que los ensayos clínicos de eficacia de los nuevos antibióticos en las agudizaciones de la bronquitis crónica se han diseñado para demostrar equivalencia, no conocemos las ventajas que pueden aportar los nuevos fármacos con mayor actividad bactericida. Mediante un análisis sistemático y un metaanálisis de ensayos publicados se pretende comparar la eficacia clínica del moxifloxacino con la de otros antibióticos utilizados habitualmente en esta indicación.

MÉTODOS: Se ha realizado una búsqueda electrónica y manual de ensayos clínicos que comparen el moxifloxacino con antibióticos de referencia para las agudizaciones de la bronquitis crónica desde enero de 1997 hasta julio de 2005. Después de verificar su adecuado diseño, se ha elaborado un metaanálisis de sus resultados clínicos.

RESULTADOS: Se identificaron 45 trabajos, de los que 9 cumplían los criterios de inclusión. Cinco eran aleatorizados y doble ciego, y 4 aleatorizados y abiertos. En total, reunieron a 3,905 pacientes. Globalmente, la diferencia media estándar en tasa de éxito clínico fue del 1,5% (intervalo de confianza del 95%, del –0,4 al 3,4%). La tasa de erradicación bacteriológica con comparadores osciló entre el 68,4 y el 96%, y con moxifloxacino entre el 87,7 y el 96%. No se observaron diferencias en las tasas de pérdidas entre los grupos de tratamiento en ningún estudio.

CONCLUSIONES: A pesar de tratarse de ensayos destinados a demostrar equivalencia, el metaanálisis realizado muestra una tendencia a la superioridad en la tasa de éxito clínico con moxifloxacino respecto a los comparadores.


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Introduction

Exacerbations of chronic bronchitis are one of the most common causes of health service use in both primary care and hospital emergency departments,1 and the management of such exacerbations incurs very high direct health-care costs.2,3 While the mean direct cost...
incurred in the treatment of an exacerbation managed outside the hospital has been estimated to be €146 per patient.\textsuperscript{4} Patients with severe exacerbations may generate a mean cost per hospitalization of over €1200.\textsuperscript{5} Although not all exacerbations are caused by bacteria, it has been observed that up to 90\% are treated with antibiotics.\textsuperscript{6} It is generally considered that empiric antibiotic therapy is indicated when an exacerbation is characterized by at least 2 of the cardinal symptoms of this entity (increase in dyspnea, sputum production, and/or sputum purulence). These are the so-called type 1 and 2 Anthonisen exacerbations.\textsuperscript{7} Although the validity of using the Anthonisen criteria to decide on initiation of antibiotic therapy has only been demonstrated in patients with moderate-to-severe chronic bronchial obstruction,\textsuperscript{8} most clinical trials of antibiotics use these criteria in patients with chronic bronchitis of any degree of severity.\textsuperscript{2}

The advent of new antibiotics for treating exacerbations of chronic bronchitis has given rise to many comparative studies with different designs, but the objective in all of them has been to demonstrate equivalence. This has given rise to a paradoxical situation in which these new antibiotics, which in vitro have advantages over the pre-existing treatments including a more appropriate spectrum and greater bactericidal capacity, appear to produce results equivalent to the standard agents in clinical trials. This paradox is an artifact of the requirements of the regulatory agencies, which only stipulate that pharmaceutical companies demonstrate that their new antibiotic is safe and that its efficacy is equivalent to that of existing treatments. Unfortunately, this demonstration of equivalence does not help the clinician to decide when and how to use the new antibiotic in preference to more traditional treatments.\textsuperscript{2}

This is the case of moxifloxacin, an 8-metoxifluoroquinolone administered orally in a single daily dose of 400 mg that has been shown to be at least as clinically effective as standard therapies in the management of exacerbations of chronic bronchitis when administered in short 5-day courses.\textsuperscript{9} The objective of the present study was to ascertain if it is possible to detect whether moxifloxacin is clinically superior to standard therapies on the basis of a systematic review of clinical trials originally designed to demonstrate equivalence.

Methods

Search for Relevant Articles

We undertook a systematic search of the PubMed database for relevant articles published between January 1, 1997 and July 2005 concerning the clinical efficacy of moxifloxacin in the treatment of patients with exacerbations of chronic bronchitis. The definition of chronic bronchitis provided by each trial was used. This entity was consistently defined as the presence of productive cough for at least 3 months in 2 consecutive years. While the definitions of an exacerbation were more varied, the patients consistently considered for inclusion in these studies were those who presented combinations of the key symptoms of exacerbation: increase in dyspnea, sputum volume, and sputum purulence with or without other minor symptoms. All of the studies considered patients with type 1 Anthonisen exacerbations for inclusion, and some also enrolled patients with type 2 or 3 exacerbations provided that they presented an increase in sputum purulence.

Statistical Analysis

Standard methods were used to estimate the effect size of the treatments using meta-analysis. The results of the main dichotomous variable were expressed as an absolute reduction in the risk of not being cured with a 95\% confidence interval. The data were analyzed with version 1.0.23 of the Comprehensive Meta-Analysis software package (www.meta-analysis.com), and a random effects model was used to calculate the aggregate value of the clinical success rate as a measure of the effect of moxifloxacin compared to the standard therapies. The random effects model was chosen because it is more conservative and because of the possible existence of variations within and between the studies caused by the different comparative treatments studied and the variations between trials in patient characteristics. In the end, as no heterogeneity was observed between the trials, the data was also analyzed using the fixed effects model, with similar results. The $\chi^2$ test was used to measure heterogeneity with statistical significance established at $P<0.05$.  

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Results

Trials Selected

The search strategy is summarized in Figure 1. The initial search yielded 45 publications. After the abstracts of these articles had been reviewed, 21 were selected for detailed review. The 24 publications excluded were review articles or letters to the editor or dealt with infections other than exacerbations of chronic bronchitis. Subsequently, 12 of the 21 trials initially selected were excluded for the following reasons: 7 were publications dealing with the same cohort, 2 were not comparative studies, and 2 were not randomized, and in 1 the groups were not parallel. In the end, we analyzed 9 studies, of which 5 were double-blind randomized trials, and 4 were open randomized trials. All the clinical trials selected had been designed to demonstrate that moxifloxacin was as effective as the comparator antibiotics.

![Figure 1. Trial selection process.](image)

**Patient Characteristics**

The main characteristics of the patients included in each of the selected trials are shown in Table 1. All of the trials enrolled patients with chronic bronchitis diagnosed according to the internationally accepted definition of presence of chronic productive cough for at least 3 months in 2 consecutive years. For the diagnosis of an exacerbation of probable infectious etiology, the inclusion criteria used by 3 trials was type 1, 2, or 3 Anthonisen exacerbation provided that an increase in sputum purulence was demonstrated; in 1 trial isolation of a respiratory pathogen in a high quality sputum sample was also required. Four trials enrolled patients with type 1 and 2 exacerbations, and the remaining trial included only patients with type 1 exacerbations. The number of patients in each study ranged from 153 to 649. The minimum age for inclusion was 18 years for all the trials except that of Wilson et al in which the minimum age was 45 years. Overall, the mean age of the patients ranged between 52 and 69 years. Lung function data were obtained in only 2 trials. In 1 trial a forced expiratory volume in 1 second (FEV1) less than 85% of predicted was used as an inclusion criterion, but 82.3% of the patients were reported to have an FEV1 under 75% of predicted. Four studies provided information on the presence of cardiopulmonary comorbidity, but no precise information was reported in any of them regarding what processes were included under this definition.

**Clinical and Microbiologic Outcomes of the Trials**

The clinical and microbiologic outcomes of the trials are shown in Table 2. The antibiotics most often chosen for comparison were the macrolides clarithromycin and azithromycin. Amoxicillin–clavulanic acid was used as a comparator in 2 trials, and levofloxacin and ceftriaxone were each used in 1 trial. One trial used 3 comparators (amoxicillin, cefuroxime, and clarithromycin). Four trials recorded the frequency of oral corticosteroid use (which ranged between 6% and 58%), but no intergroup differences in this variable were observed in any case. Neither were any significant intergroup differences observed in any trial with respect to the percentage of patients lost to follow-up.

**TABLE 1**

**Most Important Data From the Selected Studies**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Mean Age, y</th>
<th>Mean FEV1, %</th>
<th>Cardiopulmonary Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarakou et al19</td>
<td>Open</td>
<td>153</td>
<td>60.3</td>
<td>82.3% with FEV1 &lt;75%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Wilson et al15</td>
<td>Double-blind</td>
<td>750</td>
<td>60</td>
<td>NR</td>
<td>8%</td>
</tr>
<tr>
<td>Chiodosh et al14</td>
<td>Double-blind</td>
<td>936</td>
<td>55</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kreis et al11</td>
<td>Open</td>
<td>401</td>
<td>55</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>DeAbate et al10</td>
<td>Double-blind</td>
<td>464</td>
<td>55</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Huituski et al22</td>
<td>Double-blind</td>
<td>461</td>
<td>52</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Schaberg et al23</td>
<td>Open</td>
<td>577</td>
<td>60</td>
<td>NR</td>
<td>7%</td>
</tr>
<tr>
<td>Gravi et al29</td>
<td>Open</td>
<td>476</td>
<td>69.4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Wilson et al20</td>
<td>Double-blind</td>
<td>733</td>
<td>63</td>
<td>54%</td>
<td>14%</td>
</tr>
</tbody>
</table>

FEV1 indicates forced expiratory volume in 1 second. NR, not reported.
MIRAVITLLES MET AL. CLINICAL EFFICACY OF MOXIFLOXACIN IN THE TREATMENT OF EXACERBATIONS OF CHRONIC BRONCHITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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TABLE 2
Clinical Outcomes in the Selected Studies*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatments</th>
<th>Dose Regimens</th>
<th>No. of Patients</th>
<th>OC</th>
<th>Clinical Success</th>
<th>Bacteriologic Success</th>
<th>Lost to Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starakis et al</td>
<td>Moxifloxacin</td>
<td>400 mg/d, 5 days</td>
<td>79</td>
<td>NR</td>
<td>88.6%</td>
<td>90.9%</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin-clavulanic acid</td>
<td>625 mg/d, 7 days</td>
<td>74</td>
<td>NR</td>
<td>89.2%</td>
<td>70%</td>
<td>2</td>
</tr>
<tr>
<td>Wilson et al</td>
<td>Moxifloxacin</td>
<td>400 mg/d, 5 days</td>
<td>322</td>
<td>NR</td>
<td>89.1%</td>
<td>91.3%</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>500 mg/d, 7 days</td>
<td>327</td>
<td>NR</td>
<td>88.4%</td>
<td>68.4%</td>
<td>14</td>
</tr>
<tr>
<td>Chodosh et al</td>
<td>Moxifloxacin</td>
<td>400 mg/d, 5 days</td>
<td>143</td>
<td>22%</td>
<td>94%</td>
<td>89%</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>500 mg/d, 12 h, 10 days</td>
<td>129</td>
<td>19%</td>
<td>95%</td>
<td>76%</td>
<td>18</td>
</tr>
<tr>
<td>Keis et al</td>
<td>Moxifloxacin</td>
<td>400 mg/d, 5 days</td>
<td>201</td>
<td>NR</td>
<td>85%</td>
<td>90%</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin–clavulanic acid</td>
<td>625 mg/8 h, 7 days</td>
<td>74</td>
<td>NR</td>
<td>89.2%</td>
<td>70%</td>
<td>2</td>
</tr>
<tr>
<td>De Abate et al</td>
<td>Moxifloxacin</td>
<td>400 mg/d, 5 days</td>
<td>198</td>
<td>NR</td>
<td>83%</td>
<td>NR</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>500 mg/d, 12 h, 10 days</td>
<td>129</td>
<td>19%</td>
<td>95%</td>
<td>76%</td>
<td>18</td>
</tr>
<tr>
<td>Schaberg et al</td>
<td>Moxifloxacin</td>
<td>400 mg/d, 5 days</td>
<td>221</td>
<td>NR</td>
<td>88%</td>
<td>89%</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>500 mg/d, 12 h, 10 days</td>
<td>129</td>
<td>19%</td>
<td>95%</td>
<td>76%</td>
<td>18</td>
</tr>
<tr>
<td>Grassi et al</td>
<td>Moxifloxacin</td>
<td>400 mg/d, 5 days</td>
<td>227</td>
<td>9%</td>
<td>93%</td>
<td>96%</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin–clavulanic acid</td>
<td>625 mg/8 h, 7 days</td>
<td>74</td>
<td>NR</td>
<td>89.2%</td>
<td>70%</td>
<td>2</td>
</tr>
<tr>
<td>Wilson et al</td>
<td>Moxifloxacin</td>
<td>400 mg/d, 5 days</td>
<td>274</td>
<td>34%</td>
<td>69.7%</td>
<td>91.5%</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Various†</td>
<td>298</td>
<td>38%</td>
<td>62.1%</td>
<td>81%</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

OC indicates oral corticosteroids; IM, intramuscular; NR, not reported.
†The comparators were amoxicillin (500 mg/8 h), clarithromycin (500 mg/12 h), or cefuroxime (250 mg/12 h), all administered for 7 days.

TABLE 3
Clinical Success in the Subgroups of Patients With Various Risk Factors in the Trials Analyzed*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Moxifloxacin</th>
<th>Comparator</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 y</td>
<td>46/51 (90.1%)</td>
<td>47/52 (90.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;3 exacerbations in the preceding year</td>
<td>167/184 (90.8%)</td>
<td>161/181 (89.9%)</td>
<td>0.081</td>
</tr>
<tr>
<td>Cardiopulmonary comorbidity</td>
<td>22/26 (84.6%)</td>
<td>15/19 (78.9%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Concomitant use of oral corticosteroids</td>
<td>21/22 (95.4%)</td>
<td>19/20 (95.0%)</td>
<td>0.004</td>
</tr>
<tr>
<td>FEV1 % &lt;50%</td>
<td>70/119 (58.8%)</td>
<td>69/130 (53.1%)</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>66/69 (95.6%)</td>
<td>67/69 (97.1%)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

FEV1 indicates forced expiratory volume in 1 second; NS, nonsignificant differences (P values not reported in the original publication); Starakis et al, Wilson et al, Schaberg et al; Wilson et al.

Clinical Results in Patients at Risk

Four of the trials reviewed analyzed clinical outcome by the presence of various risk factors for therapeutic failure (Table 3).17,21,25,28 Intergroup differences in clinical success could not be observed in the trial carried out by Starakis and colleagues26 for any of the risk subgroups because of the small size of the sample. In a study comparing moxifloxacin and amoxicillin–clavulanic acid, Schaberg and coworkers28 found a higher cure rate with moxifloxacin (P=0.048) among patients over 60 years old and they observed a trend towards better outcomes with this antibiotic among patients with cardiopulmonary comorbidity (P=0.054). Wilson and colleagues25 reported a better clinical success rate with moxifloxacin than with clarithromycin (87.5% vs 82%; P=0.027) among patients receiving concomitant oral corticosteroid therapy. In the trial carried out by Wilson and coworkers,25 no significant differences were found in cure rates between moxifloxacin and standard antibiotic therapy when results were stratified according to corticosteroid use (oral, inhaled, or both).

Results of the Meta-Analysis

All of the trials reviewed concluded that treatment with moxifloxacin was “at least as effective” as the comparator treatment. The only exception was Wilson et al25 who reported a significantly better clinical cure rate for moxifloxacin than for the standard antibiotic therapies (69.7% vs 62.1%; 95% confidence interval [CI], 0.3%-15.6%), despite the fact that the trial was designed to demonstrate equivalence.

Analysis of the aggregate results of the 9 trials (n=3905) using a random effects model showed moxifloxacin to be associated with a 1.5% increase in the aggregate cure rate.
success rate (95% CI, –0.4% to 3.4%). Although this difference is not significant, it does however indicate a trend clearly favorable to moxifloxacin (Figure 2).

Discussion

The results of this systematic review reveal a nonsignificant trend towards a better clinical outcome in the treatment of exacerbations of chronic bronchitis with moxifloxacin as compared to the other antibiotics used routinely in such cases. This trend is of particular interest because the clinical trials reviewed were designed to demonstrate clinical equivalence. In order to put these results in context we can compare them with the results of systematic reviews evaluating the efficacy of inhaled corticosteroids in slowing down the deterioration of lung function in chronic obstructive pulmonary disease (COPD). In that case, the results reported in published reviews of multiple trials designed to demonstrate superiority have been inconsistent.43,44 As only 1 of the trials we reviewed45 included patients with COPD demonstrated by lung function16 the results cannot be extrapolated to the potential population and does not provide data on lung function, making it impossible to ascertain the severity of the exacerbation.17 As the quality of the results of this meta-analysis is determined by the quality of the trials included, certain limitations affecting these trials should be taken into account. First, the populations studied are somewhat heterogeneous. Most of them include relatively young patients and do not provide data on lung function, making it impossible to ascertain the severity of the participants’ underlying disease. In 1 trial the high consumption of oral corticosteroids for the exacerbation provided indirect evidence that the participants had

These results, together with the observation that patients with type 1 exacerbations were also at higher risk for recurrence during the 6 months following an episode and that moxifloxacin showed a nonsignificant tendency to prevent recurrence in these patients,25,26 led to the design of a new generation of clinical trials which, although still aimed at demonstrating equivalence, enrolled patients at higher risk. Another important advance has been the longer-term monitoring of patients to assess the impact of treatment on the subsequent exacerbation-free interval. This effect can be attributed to the greater bactericidal and sterilizing activity of the antibiotic agent on the bronchial infection resulting in a longer interval before recolonization and subsequent exacerbation.32,33 The study of more severe cases has made it possible to observe differences between the quinolones and the comparator therapies.32,33 But when the same kind of design is used with mild cases it is still impossible to demonstrate significant differences between quinolones and macrolides. In addition, reducing the clinical failure rate, the other primary objective of the treatment of exacerbations with antibiotics should be to prevent recurrence.34 Reducing the number of exacerbations helps reduce loss of lung function35 and slows down the deterioration of the patient’s quality of life.36 These are the results that should guide the future design of clinical trials comparing the efficacy of antibiotics in the management of exacerbations of chronic bronchitis and COPD in preference to the traditional design based on duplicating clinical trials on antibiotic use in pneumonia management.37

As the quality of the results of this meta-analysis is determined by the quality of the trials included, certain limitations affecting these trials should be taken into account. First, the populations studied are somewhat heterogeneous. Most of them include relatively young patients and do not provide data on lung function, making it impossible to ascertain the severity of the participants’ underlying disease. In 1 trial the high consumption of oral corticosteroids for the exacerbation
more severe disease. Another trial enrolled patients with more severe disease with a minimum age of 45 years and an FEV, under 85% of predicted. Secondly, the criteria used to define an exacerbation were not identical in all the studies. The earliest trials included type 3 exacerbations provided the patients’ symptoms included an increase in purulence, and the most recent trial included only type 1 exacerbations. However, in all of the trials clinical success rates were comparable and the inclusion criteria affected both treatment groups equally. Finally, in the most recently published trial it was possible to establish cure rates based on a return to the baseline situation because patients were enrolled when in a stable condition. Consequently, clinical cure results have been included in the analysis. The other 8 trials used a traditional design and enrolled patients when they presented with an exacerbation. It was not, therefore, possible in those studies to properly evaluate the clinical cure rates and the more traditional variable of clinical success was used.

Only clinical outcomes have been analyzed in this meta-analysis as these are the results that should guide choice of treatment. The reason for this is that, despite a certain degree of correlation between bacteriologic and clinical outcomes, the relationship is far from direct. In fact, in 2 of the trials significant differences were reported in bacteriologic success in favor of moxifloxacin, and in 1 trial differences were found in favor of moxifloxacin as compared to clarithromycin in the eradication of Haemophilus influenzae (94% and 78%, respectively). The results obtained in this meta-analysis indicate that it is possible and necessary to design clinical trials to demonstrate the superiority of the new antibiotics in the treatment of exacerbations of chronic bronchitis and COPD, particularly in patients with risk factors for treatment failure. Several guidelines have recognized the need to stratify patients with exacerbations according to their risk of treatment failure in order to guide the choice of antibiotic. The results of these studies will make it possible to draw up evidence-based guidelines. The primary objective is to improve treatment outcomes in patients with exacerbations so as to avert, when possible, the negative effects of these episodes on the patient’s health in the short and long term.21-23

REFERENCES


