Adverse effects of long-term azithromycin use in patients with chronic lung diseases: A meta-analysis

Running title: long-term use of azithromycin and side effects

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Abstract

The adverse effects of azithromycin on the treatment of patients with chronic lung diseases (CLD) were evaluated in the present study. MEDLINE, and other databases were searched for relevant articles till August 2013. Randomized controlled trials enrolled patients with chronic lung diseases who received long-term azithromycin treatment were selected and data on microbiological study and azithromycin-related adverse events were abstracted from articles and analyzed.

Six studies were included in the meta-analysis. The risk of bacteria resistance in patients receiving long-term azithromycin treatment was increased 2.7-fold [RR: 2.69 (95% CI 1.249, 5.211)] when compared with patients with placebo treatment. On the opposite, the risk of bacteria colonization in patients receiving azithromycin treatment decreased [RR: 0.551 (95% CI 0.460, 0.658)]. Patients with long-term azithromycin therapy were at risk of increased impairment of hearing [RR: 1.168 (95% CI 1.030, 1.325)].

This analysis provides evidence that supports the development of bacteria resistance after receiving long-term azithromycin treatment. Besides the increasingly recognized anti-inflammatory role of azithromycin used in chronic lung diseases, we should be realized the potential adverse event of its long-term use.

Key Words: Chronic lung diseases; immune modulators; azithromycin; bacterial resistance; side effect
Introduction

Recently, two reports analyzed the leading cause of death, and indicated that chronic obstructive pulmonary disease (COPD), ranked top 4 and top 3, and lung cancer, which is closely related to chronic lung inflammatory diseases, was account for the second rank and the fifth rank of years of life lost in US and China in 2010, respectively. Furthermore, compared with the declined numbers of death in patients with ischemic heart diseases and stroke, the number of patients died of COPD and lung cancer increased[1, 2]. Hence, controlling the development of chronic inflammatory lung diseases including COPD, asthma, interstitial lung diseases, bronchiectasis and cystic fibrosis have been increasingly recognized as a challengeable and necessary task for us. However, it is still far away from known how to control those diseases and millions life will be lost in the future. Chronic lung diseases (CLD) have the trend towards acute episode. For instance, patients with COPD tend towards episodes of acute exacerbations which incur decreased lung function, increased morbidity and mortality. Each exacerbation needs upgraded medications which have tremendous health economic expenditure. Despite endeavoring to relief patients with sorts of strategies, patients may still have as many as 1.4 acute exacerbations per year, averagely [3]. Therefore, any effort improving the outcome of patients with CLD will be the great step for the current situations.

Azithromycin, containing a macrocyclic 15-membered lactone ring with excellent tissue penetration and antimicrobial activity against a broad range of gram positive and gram negative bacteria [4], is widely used in the clinical settings. Besides its antibacterial activity, its anti-inflammatory roles have been increasingly recognized [3, 4]. And these years, macrolide antibiotics were explored in several clinical trials for their effects on patients with CLD including COPD, asthma, cystic fibrosis (CF) and non CF-bronchiectasis [3, 5-13]. Recently, several meta-analyses collected the data and confirmed that long-term macrolides use improving the life quality of CLD patients by improving lung-function and decreasing the frequency of acute exacerbations [14, 15]. However, no study focused on their detrimental aspect,
especially on microbiological study. To evaluate the safety of long-term azithromycin use in CLD patients, we collected randomized controlled trials evaluating the microbiological changes and azithromycin-related adverse events among patients receiving long-term use.

**Methods**

**Search Strategy**

We sought to identify all potentially relevant clinical trials using searches of web-based databases (MEDLINE [1996-2013], ISI Web of Knowledge [1996-2013], The Cochrane Central Register of Controlled Trials [1996-2013], and EMBASE). The search was performed in Aug 2013. Search terms were “azithromycin”, “(chronic lung diseases OR asthma OR COPD OR cystic fibrosis OR bronchiectasis)” and “randomized controlled trials”. Potentially relevant studies were retrieved and reviewed by 2 reviewers.

**Select criteria**

Studies were included in our analysis if they met the following criteria: (1) the design was a prospective, randomized controlled trial; (2) they performed in patients with chronic lung diseases, including COPD, asthma, cystic fibrosis, and bronchiectasis; (3) they randomized patients to a strategy of azithromycin therapy for at least three months, compared to a parallel control group; and (4) they reported one of the following outcomes: microbiological study, including newly colonization of bacteria at upper and lower respiratory tract and isolation of resistant bacteria during the study.

**Data Extraction**

Two reviewers (HL and DHL) independently extracted the following data from each study: first author, year of publication, study design, number of initially enrolled individuals, number of evaluated participants, details of azithromycin use, number of patients managed with vs. without azithromycin therapy. Data on microbiological study including newly colonization of bacteria, and macrolides resistant or overall resistant bacteria isolation during the study, mortality, hospitalization and antibiotic use during the study period, azithromycin-related side effects including...
gastrointestinal and hearing impairments were also extracted from the enrolled articles.

Regarding the assessment of the methodological quality for the included RCTs, we followed the recommendations in the Cochrane handbook for systematic reviews of interventions and summarized in a domain-based evaluation of the following components: randomization, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.

**Outcomes**

Our primary outcomes were changes in microbiological patterns and their resistance isolated from the respiratory tract between enrollment and the termination of the study. Our second outcomes were use of antibiotics, adverse events including hearing impairment and gastrointestinal reactions.

**Statistical analysis**

We assessed heterogeneity between trials using the $\chi^2$ and $I^2$ test. The $I^2$ statistic approximates the proportion of total variation in the effect size estimates that is due to heterogeneity rather than sampling error. An $I^2$ of above 25%, 50%, and 75% was taken as an indicator of mild, modest, and high heterogeneity, respectively, and a p value lower than 0.10 to be statistically significant. We calculated pooled risk ratios (RR) and 95% confidence intervals (CI) for all primary and secondary outcomes using both the Mantel-Haenszel fixed effects and the random-effects models. For all analyses, the results from the fixed-effect model are presented only when there was no heterogeneity between trials; otherwise, the results from the random-effects model are presented. Sensitivity analyses were undertook when high heterogeneity appeared.

**Results**

**Selected studies**

The process of identifying eligible studies is presented in figure 1. Search criteria identified 91 potentially relevant articles. Of these 91 articles, 73 articles due to unrelated contents, written using non-English, or other reasons were excluded from this meta-analysis (shown in figure 1). In addition, 2 studies that did not evaluate the relevant side effects, 1 RCT which run azithromycin administration under 12 weeks, 2
RCTs which had no placebo control, 1 study that analyzed the long-term effect of azithromycin for chronic rhinosinusitis, and 2 RCTs for transplanted patients were excluded from this analysis. Overall, 10 RCTs articles were remained for the further screening, and 4 studies did not collected the microbiological study including newly colonization and bacteria resistance during the observation [10-13]. Then we rule out these four studies for our analysis, since we focus our strength on the underlying adverse effect of long-term azithromycin on microbiological changes for the treated patients. Therefore, six RCTs were remained for this analysis [3, 5-9].

**Study methodology and quality**

All 6 clinical trials were identified by our research strategy as prospective randomized controlled trials (Table 1). All studies randomized patients on a 1:1 basis to either azithromycin treatment group or placebo control group. All 6 studies used intention to treat analysis to analyze their endpoint during their statistical procedure. Of these, Altenburg’s study used a modified intention to treat method, they removed data of six patients including two patients in the azithromycin group and four patients in the placebo group for the final statistical analysis, because these patients did not received the related treatment at the beginning [9]. Five studies used double-blind method for blinding treated patients, and Albert’s study was un-blinded [5-9]. Two of six studies used azithromycin according to the weight of patients, because they enrolled children in their studies [5, 6]. Another three of six studies administered the patients with azithromycin at the dose of 250mg for the different time periods [3, 8, 9]. Another one use 500mg azithromycin for their experimental groups [7]. The patients in two studies took azithromycin for one year [3, 9], and other four studies administered the patients with azithromycin for approximately 6 months [5-8]. All trials treated their control group by using the current published guidelines with same appearance placebo. Only two studies set up run-in time period of free of exacerbation that ensure the stability of the patients for at least two-weeks before enrollment [8, 9]. To exclude the influence of antibiotics therapy, five of six studies set up the exclusion criteria for patients treated with antibiotics including macrolides and quinolones for at least 14 days before enrollment [5-9]. Albert’s study did not mentioned exclusion criteria of
antibiotics use before enrollment, but patients in their study were at stable stage of COPD which had not exhibited an acute exacerbation of COPD for at least 4 weeks before enrollment [3]. Only two studies set up washout time period to exclude or investigate the influence of prolonged effect of the treatment [3, 8].

**Patient population**

A total of 1,929 patients were randomized to either azithromycin groups or placebo/control groups. Of these, 1,731 patients completed the full-course investigation. All studies declared that there were no significant differences between both study groups at baseline with respect to age, lung function, smoking history. The details of population characteristics regarding different studies were shown in table 1. Two of six trials enrolled patients including children above 6 years old for their investigations, because they worked on the long-term effect of azithromycin for patients with cystic fibrosis which is a common lethal inherited disease and developing from the early childhood among the white peoples [5, 6]. Among these six trials, there is one trial studied on patients with COPD [3] and one for patients with asthma [8]. In addition, there are two trials work on patients with non-cystic fibrosis bronchiectasis [7, 9] and the other two focused on cystic fibrosis [5, 6]. For COPD patients, the parameter of the percentage of FEV1 of predicted value indicated patients with severity from moderate to severe stage were enrolled. The others trials enrolled patients with mild to moderate impairment of lung function.

**Effect of long-term azithromycin use on the changes in microbiological pattern**

All studies performed the bacteria resistance experiments. Of these, Four studies study on the macrolides susceptibility of related bacteria isolated during the investigation, and the other two studies listed not only macrolides-resistant bacteria but also Methicillin-resistant *Staphylococcus aureus*. We collected the data regardless of different species or resistance to different antibiotics. Significant heterogeneity was found among the analyzed trials ($\chi^2=50.47$, $p<0.001$, $I^2=90.1\%$). By using M-H random-effect model, patients in azithromycin groups had positive relevance with a risk of bacteria resistance during the study period when compared with placebo groups [pooled RR: 2.597 (95% CI 1.294, 5.211), $z=2.69$, $p=0.007$]. For the sensitive
analysis, we excluded the Saiman 2010 study [6], because they reported the results of 198 bacteria colony rather than the number of patients carried with positive resistant bacteria. With a decreased heterogeneity in some degrees ($\chi^2=26.93$, $p<0.001$, $I^2=85.1\%$), the results remained stable and exhibited the same trend regarding bacteria resistance during the study period for the azithromycin-treated patients [pooled RR: 2.927 (95% CI 1.282, 6.683), $z=2.55$, $p=0.011$].

Four studies observed the newly colonized bacteria from different sites or samples, including nasopharyngeal, sputum and throat cultures. Significant heterogeneity was found among the analyzed trials ($\chi^2=64.95$, $p<0.001$, $I^2=95.4\%$). Then, random-effect analyzer was used for the further evaluation and indicated that there was no significant difference between azithromycin groups and placebo groups for the newly detected colonization during observations [pooled RR: 0.747 (95% CI 0.404, 1.381), $z=0.93$, $p=0.352$]. As study of Saiman 2010 used a different method to count the newly colonization (newly detected bacteria rather than patients with newly colonization), it might lead to the high heterogeneity and may affect the result. We then excluded this study for the analysis, and found that decreased heterogeneity existed among the studies ($\chi^2=2.25$, $p=0.325$, $I^2=10.9\%$). The further analysis indicated compared with placebo groups, patients in azithromycin group had a lower risk of newly colonization of bacteria during investigations [pooled RR: 0.551 (95% CI 0.460, 0.658), $z=6.54$, $p<0.001$].

Since it seems that patients in azithromycin groups had a trend toward carrying resistant bacteria, we wonder probably antibiotics prescription might be increased for these patients. Only two trials recorded the information of patients treated with antibiotics. In patients used with intravenous antibiotics, we found that there were no significant differences between patient either in azithromycin or in placebo groups [pooled RR: 0.784 (95% CI 0.579, 1.060), $z=1.58$, $p=0.114$]. However, patients in azithromycin groups showed a reduction in oral antibiotics use and the pooled RR value is 0.555 with a 95% CI from 0.465 to 0.664. Then, we pooled the data of the number of patients used intravenous antibiotics and oral antibiotics together to see whether there is a difference for overall antibiotics use between patients in
azithromycin groups and placebo groups. It indicated the overall antibiotics use for patients in azithromycin groups still significantly reduced compared with patients in placebo groups [pooled RR: 0.628 (95% CI 0.537, 0.735), z=5.81, p<0.001].

The comparison of azithromycin-related side effect

To analyze azithromycin-related side effect, we extracted the number of patients with gastrointestinal side effects including vomiting, abdominal pain, diarrhea, and decreased appetite from the original articles. Overall, it exhibited a high degree of heterogeneity among these trials ($\chi^2$=31.68, p<0.001, $I^2$=84.2%). Therefore, we conducted the data using random-effect model. It indicated that there were no significant differences between the patients in azithromycin groups and the patients in placebo groups for gastrointestinal side effect during the study period [pooled RR: 1.187 (95% CI 0.761, 1.849), z=0.76, p=0.450].

Then we compared the data of another reported side effect, hearing impairment. Three articles reported the relevant data and the heterogeneity test showed there was no difference among these data. The pooled RR was 1.168, with a 95% CI from 1.030 to 1.325, and indicated that compared to placebo groups, patients in azithromycin groups showed a trend towards hearing impairment after receiving long-term azithromycin therapy (z=2.42, p=0.015).

Discussion

Long-term use of macrolides was found to be effective for patients with diffuse panbronchiolitis since the late 1980s [16]. After then, its advantages have been investigated among patients with chronic lung diseases including cystic fibrosis, COPD, asthma, and non-cystic fibrosis bronchiectasis [3, 5-13]. The mechanisms for macrolides in the treatment of these diseases remains unexplained, but may be due to their antibacterial and/or anti-inflammatory actions [4], which include reductions in proinflammatory cytokines production [9-11], hastening phagocytosis ability of macrophages [17, 18]. In addition, macrolides have potentially beneficial properties including anti-viral actions [19]. However, recently research concerned the underlying adverse event of long-term macrolides therapy for patients with chronic lung diseases.
and found that patients treated with long-term macrolides could be at risk of increased infection with nontuberculous mycobacteria [20, 21]. Furthermore, some macrolides may have underlying severe side effects such as increased cardiovascular events [22]. In this analysis, we focused on the side effect of long-term use of azithromycin for patients with chronic lung diseases enrolled by randomized controlled trials. We found that long-term use of azithromycin 1) may lead to increased bacteria resistance isolated from treated patients, 2) might be decrease colonization of bacteria and antibiotic use within some extent, and 3) potentially results in hearing impairments. Hence, long-term use of azithromycin for patients with chronic lung diseases should be scrupulous in spite of its advantages of improving lung function and decreasing exacerbation of diseases.

We notice that in our analysis the result of bacteria colonization exhibits some degree of variable and seems unstable. After ruling out Saiman’s study [6], the result showed a decreased heterogeneity and indicated bacteria colonization have been reduced among patients treated with azithromycin. Presumably, the following explanation could be account for the heterogeneity and variable: 1) different methods for analyzing the bacteria colonization. In Saiman’s study [6], they counted the number of positive species rather than the number of patients colonized with bacteria. As lower respiratory tract in CF patients are rarely sterile, comparing the difference using numbers of patients colonized with bacteria between the both groups could be insignificance. 2) We also notice that the increased rate of colonization in Saiman’s study was due to the increased resistant bacteria isolated from the azithromycin-treated patients which are in accordance with the patterns of bacteria resistance analyzed for these patients. Indeed, besides resistant bacteria, other species did not show difference between the both groups. 3) *Pseudomonas aeruginosa* itself could not be killed by macrolides. However macrolides inhibit the formation of biofilm which is convenient for *P. aeruginosa’s* colonization [23]. Hence, CF patients infected with *P. aeruginosa* might be benefit from long-term azithromycin use, because long-term azithromycin use could be improve the niche in the lung of CF patients infected with *P. aeruginosa*. While long-term azithromycin use in CF patients
uninfected with *P. aeruginosa* might mediate bacteria resistance. This could interpret why the two Saiman’s studies had different microbiological results.

From our analysis, it indicates that long-term azithromycin use might be lead to increased bacteria resistance. In accordance with the most recent literature [24], patients with bronchiectasis used with azithromycin are at risk of higher macrolide resistance than that of less exposure. Meanwhile, in their report, azithromycin use was correlated with significantly reduced carriage of *S. pneumonia* (carried by about 60% of patients), *H. influenzae* and *M. catarrhalis*, however it increased the carriage of *S. aureus* and macrolide-resistant strains of *S. pneumoniae* and *S. aureus* in a cumulative dose-dependent style. This report may partly explain the results of our analysis with decreased bacteria colonization and increased bacteria resistance. As colonization of resistant bacteria in respiratory tract may not escalate the current therapy, the reduced antibiotic use in the patients treated with azithromycin might be due to the decreased frequency of exacerbation. However, resistant gene for azithromycin can be transferred between different pathogens [25]. The increased colonization of resistant bacteria may facilitate the dissemination of bacteria resistance and potentially fail the further therapy.

As a meta-analysis, we must concern on the following limitations: 1) there was a small number of available trials, as only 6 randomized controlled trials were available for this analysis; 2) there was potential publication bias in the enrolled studies since positive results are more likely to be published than negative results; 3) it might be an increase of type I error after many times of calculations.

In conclusion, long-term azithromycin use in chronic lung diseases should be scrupulous and perspective, multi-center RCT with more strict and longer period of investigation weighing the adverse effect on bacteriological changes should be explored in future.

**Statement of interest:** None declared.
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<table>
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<tr>
<th>Publication yr subjects</th>
<th>Study design</th>
<th>ITT analysis</th>
<th>Azithromycin regimen</th>
<th>Randomized patients (n)</th>
<th>Fully-compliant patients (n)</th>
<th>Age (mean ± SD or mean, IQR)</th>
<th>FEV1 % of predicted</th>
<th>FEV1/FVC</th>
<th>Newly Colonization (n)</th>
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<td>2011 COPD</td>
<td>MC, RCT, UB</td>
<td>Yes</td>
<td>250mg/d, 1 year</td>
<td>1142</td>
<td>495</td>
<td>20.2±7.9</td>
<td>70.6±23.7</td>
<td>83</td>
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<td>2003</td>
<td>Cystic fibrosis</td>
<td>Yes</td>
<td>250mg (weight &lt;40kg) or 500mg (weight&gt;40kg) of oral azithromycin 3 days a week for 168 days</td>
<td>185</td>
<td>83</td>
<td>20.6±8.6</td>
<td>80.1±18.4</td>
<td>92</td>
<td>124</td>
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<tr>
<td>2010</td>
<td>Cystic fibrosis</td>
<td>Yes</td>
<td>250mg (weight 18-35.9kg) or 500mg (weight&gt;36kg) of oral azithromycin 3 days a week for 168 days</td>
<td>263</td>
<td>125</td>
<td>10.7±3.25</td>
<td>97.6±16.6</td>
<td>68.3±21.3</td>
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<tr>
<td>2012</td>
<td>Bronchiectasis</td>
<td>Yes</td>
<td>500 mg azithromycin three times a week for 6 months</td>
<td>141</td>
<td>67</td>
<td>10.6±3.10</td>
<td>97.6±16.6</td>
<td>68.3±21.3</td>
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<td>2013</td>
<td>Asthma</td>
<td>Yes</td>
<td>250mg/d for 5 days followed by three times a week for total of 26 weeks</td>
<td>109</td>
<td>53</td>
<td>36.6±9.1</td>
<td>82.7±27.2</td>
<td>68.6±12.3</td>
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<td>2013</td>
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<td>Yes</td>
<td>250mg/d, 1 year</td>
<td>89</td>
<td>42</td>
<td>59.9±12.3</td>
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<td>Asthma</td>
<td>Yes</td>
<td>250mg/d for 5 days followed by three times a week for total of 26 weeks</td>
<td>45</td>
<td>46</td>
<td>66.8±12.3</td>
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Table 1: Characterization of enrolled trials and extracted data
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<td>resistant bacteria (n, positive/tested)</td>
<td>38/47</td>
<td>44/108</td>
<td>4/84</td>
<td>4/92</td>
<td>52/331</td>
<td>13/293</td>
<td>2/46</td>
<td>0/45</td>
<td>20/23</td>
<td>8/23</td>
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<td>Oral antibiotic use (n)</td>
<td>60</td>
<td>91</td>
<td>18</td>
<td>30</td>
<td>65</td>
<td>99</td>
<td>11</td>
<td>14</td>
<td>5</td>
<td>4</td>
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<td>IV antibiotic use (n)</td>
<td>142</td>
<td>110</td>
<td>1</td>
<td>1</td>
<td>17</td>
<td>19</td>
<td>6</td>
<td>4</td>
<td>23</td>
<td>6</td>
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<tr>
<td>Hearing impairment (n)</td>
<td>15</td>
<td>76</td>
<td>21</td>
<td>54</td>
<td>23</td>
<td>9</td>
<td>18</td>
<td>8</td>
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Note: a means Saiman’s article published on 2003, and b means Saiman’s article published on 2010 in JAMA. A means azithromycin group, and C means control group.
Figures:

Figure 1. Flow diagram depicting number of studies included at each stage of selection process.

- Potentially relevant articles identified in PubMed and the Cochrane central register of randomized controlled trials or through the review of the references of the relevant articles (n=91)
  - Articles excluded
    - Written in German (n=1), Spanish (n=2), Polish (n=1), and Chinese (n=1)
    - Non-relevant articles (n=38)
    - Review articles (n=17)
    - Editorials or comments (n=1)

- RCTs retrieved for further evaluation
  - RCTs excluded
    - RCT study protocol (n=6)
    - Open-labeled trial (n=1)
    - Other macrolides other than azithromycin (n=1)
    - Pilot study (n=4)

- RCTs regarding antibiotics used in patients with lung diseases
  - RCTs excluded
    - Azithromycin used in lung transplantations (n=2), other location (n=1)
    - Study period <12 weeks (n=1)
    - Without placebo control (n=2)
    - Without evaluating relevant side effects (n=2)
    - Without reporting microbiological study (n=4)

- Six RCTs remained for analysis.
Figure 2. Forest plot for risk ratio of bacteria resistance during investigation in azithromycin treated patients and placebo patients (A: Including all six included RCTs; B: Sensitive analysis of bacteria resistance and Saimen 2010 study was excluded).
Figure 3. Forest plot for risk ratio of newly detection of bacterial colonization in azithromycin treated patients and placebo patients (A: Including four RCTs; B: Sensitive analysis of newly colonization and Saimen 2010 study was excluded).
**Figure 4.** Forest plot for risk ratio of antibiotic use in azithromycin treated patients and placebo patients (A: Intravenous antibiotic use; B: Oral antibiotic use; C: Overall antibiotic use).
Figure 5. Forest plot for risk ratio of gastrointestinal impairment in azithromycin treated patients and placebo patients.

Figure 6. Forest plot for risk ratio of hearing impairment in azithromycin treated patients and placebo patients.