Clinical Efficacy and Correlation of Clinical Outcomes With In Vitro Susceptibility for Anaerobic Bacteria in Patients With Complicated Intra-abdominal Infections Treated With Moxifloxacin

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Background. Appropriate antimicrobial therapy results in improved clinical outcomes in complicated intra-abdominal infections (cIAIs). Recent in vitro studies have reported increasing moxifloxacin resistance of Bacteroides species, thereby cautioning empiric use in infections with these organisms.

Methods. This pooled analysis of 4 randomized clinical trials (2000–2010) evaluated the comparative efficacy of moxifloxacin in cIAIs, including infection with anaerobic organisms. The intent-to-treat population included 1209 patients who received moxifloxacin (745 microbiologically valid cases) and 1193 patients who received comparator agents (741 microbiologically valid cases).

Results. Overall clinical success rates in the per-protocol population were 85.6% (817 of 955 patients) for moxifloxacin and 87.8% (860 of 979 patients) for comparators. Of 642 pretherapy anaerobes from moxifloxacin-treated patients, 561 (87.4%) were susceptible at $\leq$2 mg/L, 34 (5.3%) were intermediate at 4 mg/L, and 47 (7.3%) were resistant at $\geq$8 mg/L. Moxifloxacin achieved similar clinical success rates against all anaerobes including those isolated from patients infected with Bacteroides fragilis (158 [82.7%] of 191 patients), Bacteroides thetaiotaomicron (74 [82.2%] of 90 patients) and Clostridium species (37 [80.4%] of 46 patients). The overall clinical success rate for all anaerobes was 82.3%. For all anaerobes combined, the clinical success rate was 83.1% (466 of 561 patients) for a minimum inhibitory concentration (MIC) of $\leq$2 mg/L, 91.2% (31 of 34 patients) for an MIC of 4 mg/L, 82.4% (14 of 17 patients) for an MIC of 8 mg/L, 83.3% (5 of 6 patients) for an MIC of 16 mg/L, and 66.7% (16 of 24 patients) for an MIC of $\geq$32 mg/L.

Conclusions. Moxifloxacin demonstrated clinical success for intra-abdominal infections caused by both aerobic and anaerobic isolates. More than 87% of baseline anaerobic isolates from intra-abdominal infections were susceptible to moxifloxacin, and efficacy was maintained beyond the current susceptibility breakpoint MIC of $\leq$2 mg/L against major anaerobes.

Intra-abdominal infections (IAIs) are common and potentially serious polymicrobial infections that are caused

Intra-abdominal infections (IAIs) are common and potentially serious polymicrobial infections that are caused by a mixture of aerobic and anaerobic bacteria that act synergistically [1, 2]. The Bacteroides fragilis group is recognized as the most commonly isolated and most pathogenic anaerobe in these infections. There is a correlation between in vitro susceptibility and clinical outcome in patients with infections caused by Bacteroides species (spp) [3–5]. Patients who receive antibiotics that are inactive against these bacteria are more likely to suffer treatment failure, manifested by recurrent infection and/or mortality. Accordingly, current guidelines for treatment of IAIs that are likely to be caused by anaerobic and facultative bacteria recommend empiric use of agents

Received 27 March 2011; accepted 17 August 2011; electronically published 12 October 2011.

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Clinical Infectious Diseases 2011;53(11):1074–80
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1058-4838/2011/5311-0005$14.00
DOI: 10.1093/cid/cir664
with documented in vitro and in vivo efficacy [2]. Complicated IAIs (cIAIs) are often polymicrobial, usually involving 2 or 3 aerobic and up to 9 anaerobic species [6, 7] and extend into the peritoneal cavity or other ordinarily sterile regions of the abdominal cavity [1]. Surgical source control has assumed an increasingly important role in the management of cIAIs [2].

Recently, the Surgical Infection Society (SIS) and Infectious Disease Society of America (IDSA) published guidelines for the treatment of IAIs [2] and recommended moxifloxacin as monotherapy for mild-to-moderate cIAIs. Studies of the in vitro activity of moxifloxacin against anaerobic bacteria have utilized strains from diverse sites of infection and without reference to previous therapy, and have shown disparate results [8–16]. Concern over the use of fluoroquinolones in IAIs has arisen following reports such as that from Golan et al [17], which highlighted the emergence of resistance among isolates (n = 4,434) of Bacteroides spp collected from US hospitals from 1994 through 2001. A closer analysis of the report revealed that investigators had used a lower breakpoint (4 mg/L) than is recommended by the Food and Drug Administration (FDA) and Clinical Laboratory Standards Institute (CLSI; 8 mg/L), making their results difficult to interpret [18]. Furthermore, only a slight increase in the geometric mean of the minimum inhibitory concentration (MIC) was found, rising from 1.36 to 1.59 mg/L for moxifloxacin. A recent update by Snyder et al [19] noted a 32% resistance rate for moxifloxacin against B. fragilis, using a breakpoint of ≥8 mg/L.

Although in vitro activity of moxifloxacin against anaerobic isolates has been the subject of various reports [9–12, 14, 16, 20–22], few investigations have used large numbers of isolates from a single anatomic site [8, 16, 20]. Goldstein et al [21] studied 923 anaerobes isolated from 2001 through 2004 and collected in a uniform manner from pretreatment cultures of patients with IAIs and, in contrast to the report by Golan et al [17], noted that 83% were susceptible to ≤2 mg/L moxifloxacin, including 85.5% of 110 B. fragilis isolates and 85.5% of 90 Bacteroides thetaiotaomicron isolates. These data are different from those in another study of B. fragilis group isolates recovered from patients with diabetic foot infections, in which only 43% of 51 isolates were susceptible to moxifloxacin [23].

The penetration of moxifloxacin into peritoneal exudates and abscesses [24, 25] and serum bactericidal levels [26] support the use of this agent for cIAIs. In order to accurately clarify the potential clinical utility of moxifloxacin in IAIs, especially in relation to anaerobic pathogens, we retrospectively analyzed pooled data from 4 randomized, controlled moxifloxacin trials [27–30] and evaluated the in vitro activity of moxifloxacin against 537 of the major anaerobic isolates obtained from 409 microbiologically valid patients (from a total of 745 microbiologically valid patients).

**PATIENTS AND METHODS**

Four controlled, randomized clinical trials evaluated the comparative efficacy of moxifloxacin in cIAIs [27–30] and were conducted between 2000 and 2010. The study design and methodology of the 4 clinical trials were similar. All studies (study 100272, Malangoni; study 10209, AIDA; study 11647, DRAGON; and study 11976, PROMISE) were multicenter, multinational clinical trials. With the exception of the AIDA trial [30], the studies had a double-blind design. Two of the studies were of intravenous therapy only [27, 29], whereas a sequential administration of intravenous therapy followed by oral therapy was permitted in the other 2 studies [28, 30]. In all 4 cIAI studies, the primary efficacy endpoint was clinical success at test-of-cure (TOC); bacteriological response was a secondary efficacy endpoint. Clinical success was based on resolution or improvement of clinical signs and symptoms related to the infection, and without the occurrence of infections requiring additional antibiotic treatment. Bacteriological response was dependent on eradication of the pathogen or pathogens from the infection site. Studies were designed as noninferiority studies using a 10% [27, 28, 30] or 15% noninferiority margin [29]. All 4 clinical trials was conducted in accordance with the Declaration of Helsinki, the International Committee for Harmonization’s Good Clinical Practice guidelines, local laws, local regulations, and institutional requirements. All patients provided written informed consent prior to the start of the study. The primary diagnosis of each patient in the 4 clinical trials was an IAI in which an operative procedure such as a laparotomy or laparoscopy (all 4 cIAI studies) [27–30] or percutaneous drainage [28–30] was required for confirmed diagnosis and management in addition to antibiotic therapy. Patients were hospitalized adults with an anticipated duration of treatment for the IAI of at least 5 days, except for those in the DRAGON study [29], which required a minimum of 3 days. Patients had a documented IAI categorized as intra-abdominal abscess; bacterial peritonitis; appendicitis with evidence of a perforation or abscess; or perforation of the stomach, duodenum, small bowel, or large bowel. For specific enrollment criteria, the reader is referred to the individual published trials [27–30]. This pooled analysis of 4 cIAI trials provides clinical and bacteriological outcomes for the per-protocol and the microbiologically valid populations (see the originally published study citations for definitions of analyses populations [27–30]).

All study centers shipped clinical isolates to a central laboratory for identification and susceptibility testing. For 3 of the cIAI studies [27–29], microbroth dilution was used for aerobes, and the agar dilution method (M11-A6) was used for anaerobes. For the AIDA study [30], the Etest was used for both aerobes and anaerobes [18]. The interpretative criteria for anaerobic breakpoints for moxifloxacin were defined according to the approved
FDA package insert and CLSI: ≤2 mg/L, susceptible; 4 mg/L, intermediate; and ≥8 mg/L, resistant [18, 31].

RESULTS

Baseline diagnostic characteristics are summarized in Table 1. Complicated appendicitis (>58% of patients) followed by peritonitis (>18% of patients) and gastrointestinal perforation without confirmation of peritonitis (11–12% of patients) were the most common diagnoses. The baseline characteristics were well balanced between the 2 groups.

Clinical Outcome

For the pooled analysis, the clinical success rates at TOC were 85.6% (817 of 955 patients) for moxifloxacin and 87.8% (860 of 979 patients) for comparator agents in the per-protocol population (Table 2). This was the primary efficacy analysis for all 4 trials. The clinical success rates for moxifloxacin met the prespecified noninferiority margin of 10% for 3 of the cIAI trials [27, 28, 30] and 15% for the DRAGON trial [29].

Bacteriological Outcome

Table 3 presents the pooled bacteriological response rates by bacterial type (aerobe, anaerobe, or mixed) at the TOC. The bacteriological response rates were similar for the 3 groupings and ranged from 81.7% to 88.5% for moxifloxacin and from 83.0% to 89.4% for the comparators. Overall, the frequencies of individual species and bacterial eradication rates were similar between moxifloxacin and comparators (Table 4). The efficacy of moxifloxacin was similar against a range of anaerobic species including B. fragilis (158 [82.7%] of 191 patients), B. thetaiotaomicron (74 [82.2%] of 90 patients), B. ovatus (23 [74.2%] of 31 patients), B. vulgatus (27 [84.4%] of 32 patients), other Bacteroides spp (50 [87.7%] of 57 patients), and Clostridium spp (37 [80.4%] of 46 patients).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Moxifloxacin, no. (%) of patients (n = 955)</th>
<th>Comparator, no. (%) of patients (n = 979)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendicitis</td>
<td>556 (58.2)</td>
<td>570 (58.2)</td>
</tr>
<tr>
<td>Peritonitis (excluding appendicitis)</td>
<td>177 (18.5)</td>
<td>187 (19.1)</td>
</tr>
<tr>
<td>GI perforation without confirmation of peritonitis</td>
<td>118 (12.4)</td>
<td>112 (11.4)</td>
</tr>
<tr>
<td>Other</td>
<td>104 (10.9)</td>
<td>110 (11.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study (years conducted; main region), treatment, dose</th>
<th>Moxifloxacin, n/N (%)</th>
<th>Comparator, n/N (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>100272, Malangoni (2000–2003; USA) Sequential (IV and PO) moxifloxacin, 400 mg QD (comparator: sequential [IV and PO] piperacillin and tazobactam, 3.0 and 0.375 g, respectively, IV every 6 hours; followed by amoxicillin clavulanate, 800 or 114 mg PO every 12 hours)</td>
<td>146/183 (79.8)</td>
<td>153/196 (78.1)</td>
<td>−7.4 to 9.3</td>
</tr>
<tr>
<td>10209, AIDA (2001–2002; EU) Sequential (IV and PO) moxifloxacin, 400 mg QD (comparator: sequential [IV and PO] ceftriaxone, 2 g IV QD, plus metronidazole, 0.5 g IV every 8 hours; followed by amoxicillin clavulanate, 500 or 125 mg PO every 8 hours)</td>
<td>199/246 (80.9)</td>
<td>218/265 (82.3)</td>
<td>−8.9 to 4.2</td>
</tr>
<tr>
<td>11647, DRAGON (2005–2007; China and Asia) Moxifloxacin, 400 mg IV QD (comparator: ceftriaxone, 2 g IV QD, plus metronidazole, 500 mg BID)</td>
<td>157/174 (90.2)</td>
<td>165/171 (96.5)</td>
<td>−11.7 to −1.7</td>
</tr>
<tr>
<td>11976, PROMISE (2006–2009; EU) Moxifloxacin, 400 mg IV QD (comparator: ertapenem, 1 g IV QD)</td>
<td>315/352 (89.5)</td>
<td>324/347 (93.4)</td>
<td>−7.9 to 0.4</td>
</tr>
<tr>
<td>Total</td>
<td>817/955 (85.6)</td>
<td>860/979 (87.8)</td>
<td>…</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; CI, confidence interval; EU, European Union; IV, intravenous; PO, oral administration; QD, once daily.

a N, total no. of patients valid per protocol; n, no. of patients with clinical success. There were no missing or indeterminate data in the per-protocol population.

b Stratified by center or cluster of center.

Protocol-defined, noninferiority α value of 10% using the Mantel-Haenszel formula for the primary analysis (per protocol).

Protocol-defined, noninferiority α value of 15% using the Mantel-Haenszel formula for the primary analysis (per protocol).
The rate of 82.6% was maintained at a group (Table 5; Figure 1). The overall bacterial eradication of 561 patients), respectively, for moxifloxacin-treated patients. Clinical success rates were 84.5% (474 of 561 patients) and 83.1% (466 of 24 patients) at MIC values of 0.03–0.06 to 16–32 mg/L; 1 was an isolate with an MIC that increased from 2 to 8 mg/L; and 1 was an isolate with an MIC that increased from 0.12 to 32.0 mg/L; 1 was an isolate with an MIC that increased from 0.03–0.06 to 16–32 mg/L; 1 was an isolate with an MIC that increased from 2 to 32 mg/L; 1 was a Klebsiella pneumoniae isolate with an MIC that increased from 0.12 to 32.0 mg/L; 1 was a B. fragilis isolate with an MIC that increased from 2 to 8 mg/L; and 1 was a Pseudomonas aeruginosa isolate with an MIC that increased from 1 to 8 mg/L (no breakpoint exists for moxifloxacin and P. aeruginosa).

Correlation of Anaerobic In Vitro Susceptibility Data and Outcomes

For all anaerobes, the bacteriological eradication and clinical success rates for moxifloxacin were consistent with the existing CLSI and FDA susceptibility criteria [18, 31]. In the susceptible category of ≤2 mg/L, the bacteriological eradication and clinical success rates were 84.5% (474 of 561 patients) and 83.1% (466 of 561 patients), respectively, for moxifloxacin-treated patients (Table 5). Figure 1 shows the clinical success rate by MIC value, as well as the frequency of bacterial isolates at each MIC. The overall clinical success rate of 82.3% was maintained well beyond the susceptible category of ≤2 mg/L out to 16 mg/L (83.3%), with a decrease to 66.7% (16 of 24 patients) at MIC values of ≥32 mg/L in the moxifloxacin group (Table 5; Figure 1). The overall bacterial eradication rate of 82.6% was maintained at >80% out to the breakpoint of ≤4 mg/L, with a decrease to ≤70.6% at MIC values of ≥8 mg/L (Table 5; Figure 2).

**DISCUSSION**

The pooled results from 4 well-controlled clinical trials of cIAIs are reported. This database for anaerobic MIC values correlated to clinical outcome represents possibly the largest dataset reporting such correlations.

Overall clinical success rates were consistent with expected patterns for IAIIs and are similar to the clinical success rates reported in recent cIAI studies [32, 33]. Efficacy was also demonstrated against the major anaerobic species in IAIIs, including Bacteroides spp and Clostridium spp. In contrast to recently published in vitro studies that noted rising moxifloxacin resistance among Bacteroides spp [34–36], only 16 (5.5%) of 289 intra-abdominal B. fragilis and B. thetaiotaomicron isolates were resistant to moxifloxacin (MIC, ≥8 mg/L) in these trials.

Antibacterial therapy in IAIIs offers a rare opportunity to determine the drug performance against the entire MIC range of a particular bacterial genus and species. Antimicrobial therapy in IAIIs is typically initiated empirically, well before the bacterial pathogens have been identified or tested for susceptibility, as was done in the 4 controlled IAI trials presented here [27–30].

This pooled analysis supports the contention that moxifloxacin is efficacious for the treatment of cIAIs caused by a broad range of anaerobic and aerobic bacteria. Clinical success was maintained at a rate of >80% for moxifloxacin at MIC values of ≤8 mg/L for all anaerobes, including the major
individual anaerobic species. Bacteriological response was maintained at a rate of approximately 80% for moxifloxacin at MIC values of ≤4 mg/L. Our data support the published SIS and IDSA guidelines [2], which recommend moxifloxacin as monotherapy for the treatment of mild-to-moderate community-acquired cIAIs.

Resistance in *B. fragilis* group isolates to all antimicrobial agents, including carbapenems, piperacillin-tazobactam, and even metronidazole, is of concern worldwide [37]. However, reliance only on published MIC surveys can be confusing and clinically misleading. Several in vitro studies reported resistance in *B. fragilis* group species to moxifloxacin in the range of 32.1% for *B. fragilis* and 33% for *B. thetaiotaomicron* in a multicenter US study [17, 36] and 30% and 75%, respectively, in a study in Athens, Greece [35]. Other in vitro data show that moxifloxacin has maintained reliable activity against anaerobes [34, 38]. From South Korea, Lee et al [34] reported that recent (2007–2008) *B. fragilis* group isolates had a 4% and 7% resistance rate to imipenem and piperacillin-tazobactam, respectively, whereas the moxifloxacin resistance rate was 11% for *B. fragilis* and 18% for other *B. fragilis* group isolates. Overall, the trend is for increasing moxifloxacin and fluoroquinolone MIC values against anaerobes.

MIC results for anaerobes can be affected by local clonal populations, local antimicrobial usage patterns, anaerobic in vitro susceptibility testing methods, and site of isolation [39]. Results of single-site isolates from pretherapy IAI specimens clearly show a difference from those above using multiple-source isolates without regard to prior therapy. Goldstein et al [21] studied 923 anaerobes isolated only from IAIs and collected from 2001 through 2004, and by use of the agar dilution method found that moxifloxacin was active against 97 (88%) of 110 *B. fragilis* strains and 78 (87%) of 90 *B. thetaiotaomicron* strains at the current breakpoint of ≤2 mg/L. More recently, Seifert and Dalhoff [40] used the broth microdilution method and reported that in a German survey of anaerobes collected in 2007 solely from intra-abdominal sources, only 3 (1%) of 238 *B. fragilis* isolates were resistant to metronidazole, 8% of *B. fragilis* isolates were resistant to the carbapenems, and 14% of isolates were resistant to moxifloxacin.

Several studies have suggested the importance of the antimicrobial susceptibility of the *B. fragilis* group in predicting the clinical outcome of infection [3, 5, 41]. Although extrapolation of in vitro and pharmacokinetic/pharmacodynamic data to the clinical situation may be used, patient outcome data showing the

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**Table 5. Bacteriological Eradication and Clinical Success Rates at Test-of-Cure by Pretherapy Moxifloxacin Minimum Inhibitory Concentration (MIC) for All Anaerobes in the Pooled Studies of Complicated Intra-abdominal Infection in the Microbiologically Valid Population for Moxifloxacin-treated Patients**

<table>
<thead>
<tr>
<th>MIC for all anaerobes, mg/L</th>
<th>Bacteriological eradication, n/N (%)</th>
<th>Clinical success, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.06</td>
<td>26/33 (78.8)</td>
<td>25/33 (75.8)</td>
</tr>
<tr>
<td>0.125</td>
<td>32/34 (94.1)</td>
<td>30/34 (88.2)</td>
</tr>
<tr>
<td>0.25</td>
<td>94/105 (89.5)</td>
<td>91/105 (86.7)</td>
</tr>
<tr>
<td>0.5</td>
<td>138/167 (82.6)</td>
<td>136/167 (81.4)</td>
</tr>
<tr>
<td>1.0</td>
<td>102/120 (85.0)</td>
<td>102/120 (85.0)</td>
</tr>
<tr>
<td>2.0</td>
<td>82/102 (80.4)</td>
<td>82/102 (80.4)</td>
</tr>
<tr>
<td>4.0</td>
<td>31/34 (91.2)</td>
<td>31/34 (91.2)</td>
</tr>
<tr>
<td>8.0</td>
<td>12/17 (70.6)</td>
<td>14/17 (82.4)</td>
</tr>
<tr>
<td>16.0</td>
<td>4/6 (66.7)</td>
<td>5/6 (83.3)</td>
</tr>
<tr>
<td>≥32.0</td>
<td>16/24 (66.7)</td>
<td>16/24 (66.7)</td>
</tr>
<tr>
<td>Not determined</td>
<td>9/19 (47.4)</td>
<td>12/19 (63.2)</td>
</tr>
<tr>
<td>Total</td>
<td>546/661 (82.6)</td>
<td>544/661 (82.3)</td>
</tr>
</tbody>
</table>

All samples collected before therapy in each complicated intra-abdominal infection study up to day 2 after the start of treatment were defined as pretherapy samples. Intermediate MICs have been rounded up to the nearest doubling dilution. Bacteriological eradication is defined as eradication and presumed eradication; clinical success is defined as clinical cure, resolution, and continued cure or continued resolution.

* A patient with multiple isolates from the same species is counted with all isolates in this table.

* N, total number of isolates from the intra-abdominal infection site with a bacteriological or clinical success at the test-of-cure visit; n, number of isolates with a bacteriological eradication or clinical success.

**Figure 1.** Clinical success rates for moxifloxacin-treated patients at test-of-cure by pretherapy moxifloxacin minimum inhibitory concentration (MIC) for all anaerobes in the pooled studies of complicated intra-abdominal infection (microbiologically valid population for moxifloxacin-treated patients).
correlation between clinical success and anaerobic in vitro susceptibilities remain the gold standard.

Moxifloxacin showed a numerically lower clinical response rate to B. ovatus of 71.9% (23 of 32 patients) than that shown by the combined comparators of 88.0% (22 of 25 patients). With these small numbers, it is not possible to determine the significance of the response to this 1 species.

The results of this report pooling 4 well-controlled cIAI trials [27–30], and the correlation of the MIC and clinical efficacy data, support the conclusion that moxifloxacin is clinically efficacious in the therapy of these infections. Moxifloxacin clinical success was maintained beyond the FDA and CLSI anaerobic susceptible breakpoint of ≤2 mg/L; clinical success was maintained against anaerobes up to an MIC of 8 mg/L, and bacteriological response was maintained up to an MIC of 4 mg/L. Less than 6% of the anaerobic isolates were resistant to moxifloxacin according to CLSI and FDA criteria (≥8 mg/L). The overall development of resistance for moxifloxacin during the treatment of cIAI was very low at <1% (6 of 955 treated patients). When selecting empirical antimicrobial therapy for IAI, clinicians should take into account clinically correlated MIC efficacy data from single sites of infection in well-controlled, evaluator-blinded clinical trials.

Notes

Acknowledgments. Highfield Communication Consultancy (funded by Bayer Schering Pharma) provided editorial assistance in the preparation of this manuscript.

Financial support. This work was supported by Bayer HealthCare AG and by the R. M. Alden Research Laboratory.

Potential conflicts of interest. E. C. G. has served on advisory boards of Merck, Optimer Pharmaceuticals, Theravance, and Bayer; has served on the speaker’s bureau for Bayer, Merck, and Pfizer; and has received research grants from Merck, Optimer Pharmaceuticals, Theravance, Cubist Pharmaceuticals, Pfizer, Astellas, Cerexa, Impex Pharmaceuticals, Autogenomics, Genzyme, GL Synthesis, Novartis, and Romark Labs. D. M. C. has served on the Cubist Pharmaceuticals speaker’s bureau. J. S. S. is a consultant for Bayer, Merck, Tetraphase, Novartis, Paratek, Basilea, and GSK; has received laboratory research support from Pfizer; and has received honoraria for ex-US lectures provided by Bayer, Merck, and Johnson and Johnson. J. D. A. is an employee and stockholder of Bayer HealthCare Pharmaceuticals.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


