SHORT COMMUNICATION

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Eosinophilic Pneumonia in Patients Treated with Daptomycin

Review of the Literature and US FDA Adverse Event Reporting System Reports

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Abstract

Background: Eosinophilic pneumonia (EP) has been noted in association with daptomycin use. The product labelling was recently updated to include EP in the Warnings and Precautions and Post-Marketing Experience sections.
Objective: The objective of this study was to analyse adverse event (AE) reports submitted to the US FDA as well as published cases to characterize the clinical features and course of EP in daptomycin-treated patients.
Methods: We searched for EP cases associated with daptomycin administration in the FDA Adverse Event Reporting System (AERS) submitted from 2004 to 2010, and the published literature. Cases were defined as definite, probable, possible and unlikely in terms of the diagnosis of EP and the potential association with daptomycin exposure. Definite cases had concurrent exposure to daptomycin, fever, dyspnoea with increased oxygen requirement or required mechanical ventilation, new infiltrates on chest imaging, bronchoalveolar lavage with >25% eosinophils and clinical improvement following daptomycin withdrawal. Additionally, we assessed inpatient daptomycin utilization.
Results: We identified 7 definite, 13 probable, 38 possible cases of daptomycin-induced EP, and 23 unlikely cases. The seven definite EP cases had resolution after daptomycin was stopped, including two with EP recurrence following daptomycin rechallenge. Regarding the definite cases: (i) ages ranged from 60 to 87 years; (ii) dosing ranged from 4.4 to 8.0 mg/kg/day; and (iii) EP developed 10 days to 4 weeks after starting daptomycin. There was a gradual increase in the number of patients with an inpatient hospital discharge billing for daptomycin from the year 2004 to 2010.
Conclusions: We report 7 definite, 13 probable and 38 possible EP cases associated with daptomycin administration. As AERS is based on voluntary

reporting, the incidence of EP cannot be assessed. Healthcare providers should have heightened awareness of this serious AE associated with daptomycin use.

Background

The daptomycin product labelling has listed pulmonary eosinophilia as an adverse event (AE) in the Post-Marketing Experience section since 2007.[1] In March 2010, Lal and Assimacopoulos[2] described two patients who developed eosinophilic pneumonia (EP) in association with daptomycin administration. In July 2010, the US FDA issued a safety communication regarding cases of EP associated with daptomycin administration.[3] The product labelling was recently updated to include EP in the Warnings and Precautions and Post-Marketing Experience sections.[4]

Daptomycin is a cyclic lipopeptide antibacterial drug[5] and is approved by the FDA for the treatment of (i) complicated skin and skin structure infections caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis* and *Enterococcus faecalis* (vancomycin-susceptible isolates only) at a dose of 4 mg/kg every 24 hours intravenously; and (ii) *Staphylococcus aureus* bloodstream infections (bacteraemia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates at a dose of 6 mg/kg every 24 hours intravenously.[4] Notably, daptomycin is not indicated for the treatment of pneumonia.[4] Pertel et al.[6] reported in the literature that the non-inferiority of daptomycin to ceftriaxone for the treatment of community-acquired pneumonia was not demonstrated in phase III trials. *In vitro* work suggests that the drug's lack of efficacy in the treatment of pneumonia can be attributed to its interaction with pulmonary surfactant.[7]

This paper describes the clinical features and course of EP in daptomycin-treated patients reported to the FDA Adverse Event Reporting System (AERS), and reviews the cases reported in the literature thus far.

Methods

We performed a standardized Medical Dictionary for Regulatory Activities (MedDRA®) query[8] for interstitial lung disease (ILD) to retrieve all US and non-US postmarketing AE reports of EP in patients treated with daptomycin submitted to AERS from 2004 to 2010. For example, 'Eosinophilic Pneumonia', 'Eosinophilic Pneumonia Acute' and 'Eosinophilic Pneumonia Chronic' are specific preferred terms (PTs) for EP in the ILD standardized MedDRA® query. However, our search was not limited to the aforementioned PTs. We performed our first search for daptomycin-associated ILD reports in February 2010. We performed a follow-up search in October 2010 to assess for new reports after the daptomycin label was updated in August 2010. We reviewed the English-language scientific literature for additional cases.

All cases were independently reviewed by two authors (PK and AS). Cases were categorized as being definite, probable, possible and unlikely in terms of the diagnosis of EP and the potential association with daptomycin exposure. The criteria used to classify cases are listed in table I. Criteria for the diagnosis of definite EP were established based on literature sources.[9-15]

In addition to the case review, a disproportionality analysis (henceforth referred to as a 'data mining analysis') of the AERS database was performed using Empirica Signal® software (Oracle, Redwood Shores, CA, USA) and the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm.[16] MGPS generates adjusted relative reporting ratios, also known as Empirical Bayes Geometric Mean (EBGM) values, for the entire AERS database. The EBGM values indicate the varying strength of reporting relationships among all drug-AE combinations in the database, including the association between 'daptomycin' and 'eosinophilic pneumonia'. The EBGM value provides a stable estimate of the relative report-

Table I. Criteria for inclusion as definite, probable, possible and unlikely in terms of the diagnosis of eosinophilic pneumonia and the potential association with daptomycin exposure

Definite
Concurrent exposure to daptomycin
Fever
Dyspnoea with increased oxygen requirement or requiring mechanical ventilation
New infiltrates on chest x-ray or CT scan
Bronchoalveolar lavage with >25% eosinophils
Clinical improvement following daptomycin withdrawal
Probable
Concurrent exposure to daptomycin
Dyspnoea with increased oxygen requirement or requiring mechanical ventilation
New infiltrates on chest x-ray or CT scan
Bronchoalveolar lavage with ≤25% eosinophils OR peripheral eosinophilia[a]
Clinical improvement following daptomycin withdrawal
Possible
Concurrent exposure to daptomycin
New infiltrates on chest x-ray or CT scan
Clinical improvement following daptomycin withdrawal OR the patient died
Unlikely
All other cases that did not meet the above criteria

a Peripheral eosinophilia is defined as a peripheral blood eosinophil level greater that the upper limit of normal for the reporting laboratory, or the reporter noted an elevated blood eosinophil level but did not provide the actual laboratory value.

ing ratio of any AE for a particular drug relative to all other drugs and AEs in AERS. MGPS also calculates lower and upper 90% confidence intervals for the EBGM scores, denoted as EB05 and EB95, respectively. The higher the EBGM value for a particular drug-AE combination, the higher is the reporting association between that drug and AE in the database. For our analysis, we focused on drug-AE pairs having an EB05 (lower bound of the 90% CI for the EBGM) ≥2, because these are events that occur at least twice the expected rate, given the data.

We used Surveillance Data Inc. (SDI), Inpatient Healthcare Utilization System (IHCarUS)[17] to examine the nationally projected estimates of unique patients who were billed for daptomycin during an inpatient hospital stay from January 2004 through December 2010. The data are gathered from a select sample of over 650 US hospitals, and projected nationally to represent all US acute-care inpatient hospitals.

Results

Case Review

As noted in the Methods section, we performed two AERS searches for ILD among patients treated with daptomycin. The search in February 2010 yielded 63 patients, and the second search in October 2010 (after the daptomycin label change) yielded an additional 14 patients. Of these 77 ILD reports in AERS, 5 met our case definition for definite, 10 for probable, 38 for possible and 24 unlikely in terms of the diagnosis of EP and the potential association with daptomycin exposure. We later reclassified 1 of the 24 unlikely cases to definite EP associated with daptomycin exposure based on additional information provided in a recently published report of the case.[18] Additionally, we identified one definite and three probable EP cases in the published literature that were not reported to AERS.[13,19,20]

In total, seven patients fulfilled the case definition for definite EP associated with daptomycin exposure (see table II). All seven cases had resolution of EP after daptomycin was stopped, including two cases that had recurrence of EP following daptomycin rechallenge. These patients subsequently recovered after daptomycin was again discontinued. One of the seven cases had a lung biopsy with pathology consistent with EP. Six of the seven cases were from the US and all were treated with daptomycin for non-FDA approved indications (osteomyelitis [n = 4], aortic valve endocarditis [n = 2] and prosthetic hip infection [n = 1]). Their ages ranged from 60 to 87 years and six were males. Dosing information was available in six of the seven patients and ranged from 4.4 to 8.0 mg/kg/day. EP symptoms developed 10 days to 4 weeks after starting daptomycin therapy. Remedial therapy with systemic corticosteroids was reported in five of the seven cases.

Table III contains information on 13 probable cases of EP associated with daptomycin exposure. These patients met all the criteria in the definite

Table II. Characteristics of the seven daptomycin-treated patients with definite eosinophilic pneumonia

Case no.	Age (y)/sex	Indication	DAP daily dose (mg/kg)	Duration of DAP at symptom onset (wks)	Clinical signs, symptoms and other findings	BAL eosinophilia (%)	Remedial therapy	Outcome
1	63/F	MSSA spinal osteomyelitis	6	3	Fever, cough, hypoxaemia; PE = 10–11%; elevated CPK	60–70	DAP d/cd; corticosteroids initiated	Recovered
2[13] a,b	60/M	MSSA endocarditis	NR	2	Fever, respiratory decline requiring MV; symptoms recurred within 4 h of rechallenge	26	DAP d/cd; corticosteroids initiated	Recovered after rechallenge
3[2]	87/M	Chronic osteomyelitis of prosthetic knee joint	4.4	4	Fever and dyspnoea requiring O_2; PE = 12%; CT showed bilateral infiltrates with ground glass consolidation	40	DAP d/cd; oxygen and long-term corticosteroids initiated	Improved, but required long-term corticosteroid therapy
4[19] a	60/M	MSSA prosthetic hip joint infection	6	2	Initially presented with fever and dyspnoea with an increased O_2 requirement, and diffuse pulmonary infiltrates on CT. DAP withheld, then restarted. Signs/symptoms resumed within 2 days of DAP rechallenge	81	DAP d/cd; corticosteroids initiated	Recovered after DAP rechallenge
5[14]	65/M	MRSA vertebral osteomyelitis and epidural abscess	6	2	Fever, dyspnoea requiring MV, PENQ; CT revealed bilateral infiltrate with peripheral predominance and sparing of bases, small bilateral effusions; lung biopsy = organizing pneumonia with many eosinophils; improved within 72 h off DAP; had 6-week taper of corticosteroids post-hospitalization	33	DAP d/cd; mechanical ventilation and IV corticosteroids initiated	Recovered, repeat CT at 3 mo was normal
6	64/M	*Staphylococcus aureus* osteomyelitis with concurrent bacteraemia	5.7	4	Fever, dyspnoea, hypoxia, PENQ, peripheral pulmonary infiltrates on imaging	44	DAP d/cd	Recovered
7[18] c	78/M	Aortic valve endocarditis	8	1.4	Fever, hypoxia, bilateral ground glass peripheral opacities with effusions on CT	27.5	DAP d/cd	Recovered

a Rechallenge case.

b Not reported to the FDA AERS.

c Originally classified as unlikely based on AERS report, but further clarified in the literature.

AERS = Adverse Event Reporting System; **BAL** = bronchoalveolar lavage; **CPK** = creatine phosphokinase; **CT** = chest CT; **DAP** = daptomycin; **d/cd** = discontinued; **F** = female; **IV** = intravenous; **M** = male; **MRSA** = methicillin-resistant *Staphylococcus aureus*; **MSSA** = methicillin-sensitive *Staphylococcus aureus*; **MV** = mechanical ventilation; **NR** = not reported; **O_2** = oxygen; **PE** = peripheral eosinophilia; **PENQ** = peripheral eosinophilia reported but not quantified.

Table III. Characteristics of the thirteen daptomycin-treated patients with probable eosinophilic pneumonia

Case no.	Age (y)/sex	Indication	DAP daily dose (mg/kg)	Duration of DAP at symptom onset (wks)	Clinical signs, symptoms and other findings	Remedial therapy	Outcome
1[19] [a]	60/M	Osteomyelitis and septic arthritis of foot	6	2	Fever, hypoxia, non-productive cough; PE = 9%; CT = peripheral nodular and ground glass changes; BAL not reported; DAP rechallenge 5 mo later and signs/symptoms recurred in 3 days	DAP d/cd	Recovered
2[19]	83/M	Lumbar diskitis	6	4	Progressive dyspnoea, cough; PE = 14.7%; CT showed diffuse ground glass and reticular opacities; lung biopsy revealed acute organizing pneumonia with eosinophilia, chronic inflammation and fibro-inflammatory changes	DAP d/cd; corticosteroids initiated	Recovered
3[20]	54/M	MRSA infection of inguinal hernia repair	NR	2	Fever, dry cough, increased O_2 requirement; PENQ; CT showed bilateral reticulonodular infiltrates; lung biopsy revealed organizing diffuse pneumonia with eosinophilic infiltrates	DAP d/cd; corticosteroids initiated	Recovered
4[2]	82/M	*Streptococcus mitis* prosthetic joint infection	NR	3	Fever, dyspnoea requiring BIPAP, PENQ, CXR and CT = patchy bilateral infiltrates, BAL = 14% eosinophils	DAP d/cd; corticosteroids initiated	Improved but required long-term corticosteroids
5	79/M	Enterococcal endocarditis	6	6	Fever, cough, night sweats, dyspnoea, progressed to need MV, CT = extensive ground glass opacities, PE = 1500; BAL = 9–13% eosinophils and lung biopsy consistent with eosinophilic pneumonitis	DAP d/c'd; corticosteroids initiated	Improved
6	26/M	MRSA bacteraemia	7.35	1.4	PENQ, new pulmonary infiltrates, eosinophils in tracheal aspirate, required increased MV	DAP d/cd	Improved
7	43/M	MRSA osteomyelitis	6	1–2	Pleuritic pain progressed to hypoxia (87% on RA) requiring O_2, bilateral infiltrates on CT, PE = 6.6% on third hospital day	DAP d/cd, NSAIDs, meperidine, but no corticosteroids	Improved, residual infiltrates on CT 1 mo later
8	66/M	MSSA bacteraemia	6	1	Progressive dyspnoea with increased O_2 requirement, haemoptysis, PENQ, BAL with eosinophils but not quantitated	ICU admit, DAP d/cd, corticosteroids initiated	Recovered
9	71/M	MRSA diabetic foot infection	4	7.7	Afebrile, dyspnoea requiring O_2, CT = bilateral interstitial opacities, PE = 8%, no BAL, ESR = 123, CRP = 75	DAP d/cd	Improved

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Table III. Contd

Case no.	Age (y)/sex	Indication	DAP daily dose (mg/kg)	Duration of DAP at symptom onset (wks)	Clinical signs, symptoms and other findings	Remedial therapy	Outcome
10	77/F	Enterococcal bacteraemia	5	1	Dyspnoea requiring O_2, PENQ, rash, CXR read as consistent with pneumonitis, no BAL or lung biopsy	DAP d/cd; corticosteroids initiated	Improved
11	67/M	MRSA endocarditis	6	4.3	Required MV, CT = bilateral pulmonary infiltrates, PENQ, BAL = 9% eosinophils	DAP d/cd; corticosteroids initiated	Improved
12	73/M	MRSA prosthetic joint infection	5	3.7	Fever, required MV, CT = bilateral ground glass appearance, PENQ	DAP d/cd; corticosteroids initiated	Recovered
13	81/F	MRSA paraspinal abscess	6	1.6	CXR = bilateral mid-lung infiltrates, required MV, BAL = 2% eosinophils (received corticosteroids prior to BAL)	DAP d/cd; corticosteroids initiated	Improved, weaned off MV in LTCF

a Rechallenge case.

BAL = bronchoalveolar lavage; **BIPAP** = bilevel positive airway pressure; **CRP** = C-reactive protein; **CT** = chest CT; **CXR** = chest x-ray; **DAP** = daptomycin; **d/cd** = discontinued; **ESR** = erythrocyte sedimentation rate; **F** = female; **ICU** = intensive care unit; **LTCF** = long-term care facility; **M** = male; **MRSA** = methicillin-resistant *Staphylococcus aureus*; **MSSA** = methicillin-sensitive *Staphylococcus aureus*; **MV** = mechanical ventilation; **NR** = not reported; **O_2** = oxygen; **PE** = peripheral eosinophilia; **PENQ** = peripheral eosinophilia reported but not quantified; **RA** = room air.

category with the exception that there was no account of fever, they had ≤25% eosinophils on bronchoalveolar lavage (BAL) and/or had only peripheral eosinophilia. Their ages ranged from 26 to 83 years (mean = 66.3 years) and 11 were males. Daptomycin dosing ranged from 4 to 7.35 mg/kg/day. Three patients had undergone lung biopsies with pathology that appeared to be consistent with EP. All improved or recovered after daptomycin was stopped and 9/13 (69%) were prescribed systemic corticosteroids. At least two cases had prolonged respiratory complications following withdrawal of daptomycin, one of which was noted to have required long-term corticosteroid maintenance therapy.[2]

There were 38 possible cases of EP associated with daptomycin administration. These cases had concurrent exposure to daptomycin, new infiltrates on chest imaging and either experienced clinical improvement with daptomycin withdrawal or died during the course of remedial treatment. Of note, five of the possible cases had BAL specimens with eosinophilia that ranged up to 70% and two had lung biopsies with pathology that appeared to be consistent with EP; however, missing data precluded further categorization. One of the patients with a lung biopsy result consistent with EP died; however, not enough information was provided in the report to determine the cause of death.

Data Mining

Although the main analysis in this paper was based on case finding using the ILD SMQ (Standardized MedDRA® query) [which includes but is not limited to the PT of 'Eosinophilic Pneumonia'] and literature review, we present data mining analyses using the single MedDRA® PT of 'Eosinophilic Pneumonia' (figure 1 and table IV). Figure 1 is a bar graph of the EBGM values for the top 24 drug products with EB05 values greater than 2.0 that have been listed in combination with the PT of 'Eosinophilic Pneumonia' in AERS reports as of 30 September 2010. Table IV contains the EBGM, EB05 and EB95 values for the nine antimicrobial agents listed in

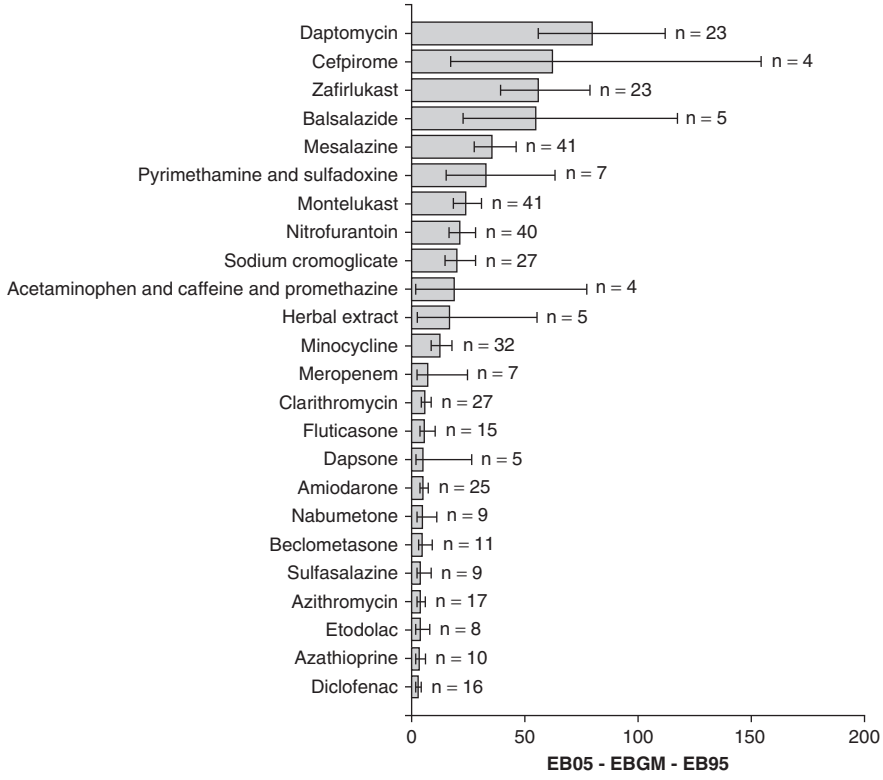

Fig. 1. Comparative EBGM scores for drug products reported with the MedDRA® preferred term of 'Eosinophilic Pneumonia' in AERS reports through quarter 3, 2010. The bar graph contains the values of N as well as the EB05 and EB95 and the EBGM value (represented by the length of the grey bars). All of the listed drug products have EB05 values greater than 2.0. Higher scores are considered potential safety signals for further assessment. Only the daptomycin reports were reviewed for potential causality and duplicate submission. **AERS** = Adverse Event Reporting System; **EB05 and EB95** = lower and upper 90% confidence intervals for the EBGM; **EBGM** = Empirical Bayes Geometric Mean; **MedDRA®** = Medical Dictionary for Regulatory Activities; **N** = number of AERS reports.

figure 1 that were disproportionately reported with the PT of 'Eosinophilic Pneumonia' in AERS.

As noted in figure 1 and table IV, daptomycin had the highest disproportionate reporting with the PT of 'Eosinophilic Pneumonia', among all drugs and specifically among antimicrobial agents, with EBGM and EB05 values equal to 80.5 and 56.2, respectively. The second drug product on the list was cefpirome, a fourth-generation cephalosporin that is not marketed in the US. Other antimicrobial agents had much lower EBGM and EB05 values, including pyrimethamine used in combination with sulfadoxine (not currently marketed in combination in the US), nitrofurantoin, minocycline, meropenem, clarithromycin, dapsone, and azithromycin. Therefore, the data mining analysis provided supporting evidence of a potential safety signal for the PT of 'Eosinophilic Pneumonia' in patients treated with daptomycin, based on disproportionate reporting in the cumulative data, as reflected by the EBGM values. Further analysis of trends for the other drugs noted in figure 1 and table IV are beyond the scope of the current study.

Inpatient Daptomycin Utilization

Using SDI, IHCarUS,[17] we examined the nationally projected estimates of unique patients who were billed for daptomycin during an inpatient hospital stay from January 2004 through December 2010. We observed that approximately

509 808 projected unique patients were billed for daptomycin during an inpatient hospital stay between the full calendar years 2004 and 2010, cumulative. There was a gradual increase in the number of patients billed for daptomycin from 12 668 unique patients in 2004 to 143 231 unique patients in 2010.

Follow-Up Since October 2010

Using Empirica Signal®, we conducted a follow-up analysis of AERS data limited to the single PT of 'Eosinophilic Pneumonia' among daptomycin-treated patients. Based on cumulative quarterly data through the third quarter of 2011, there was a continued consistent trend of disproportionate reporting for the PT of 'Eosinophilic Pneumonia' among daptomycin-treated patients, as indicated by EBGM and EB05 values equal to 156 and 125, respectively. Based on monthly drug utilization data extending to June 2011, we have not identified any appreciable differences in the trend of daptomycin utilization before or after the daptomycin label change.

Discussion

EP is characterized by eosinophilic infiltration of the pulmonary parenchyma and may present with varying severity, ranging from nearly asymptomatic infiltrates to acute respiratory distress syndrome necessitating mechanical ventilation.[11] Acute EP typically presents as a febrile illness of less than 3 weeks' duration, and in most cases the duration of symptoms is less than 7 days.[15] It is accompanied by constitutional symptoms, most importantly, non-productive cough and dyspnoea. Initial diagnostic studies may show hypoxaemia, infiltrates on chest imaging and, variably, peripheral eosinophilia. In drug-induced EP, removal of the offending agent and treatment with corticosteroids often results in rapid clinical improvement.[12]

Acute EP is a distinct respiratory syndrome that may be idiopathic, but, more recently, has been linked to drug and toxin exposures.[10,12] Before making a definitive diagnosis of acute EP, it is necessary to rule out other etiologies known to cause pulmonary eosinophilia, such as helminthic and fungal infections, other drug or toxin exposures, and allergic reactions. As noted by Allen,[10] the pathophysiology is believed to be due to the presentation of antigen (from the offending drug or pathogen) by alveolar macrophages. This is thought to result in T-helper 2 (T_h2) lymphocyte recruitment and subsequent release of interleukin (IL)-5. IL-5 from T_h2 lymphocytes promotes eosinophil production and migration to the lungs. Eosinophil localization to the lungs is also stimulated by eotaxin production from activated alveolar macrophages. Hayes et al.[13] hypothesized that daptomycin may cause acute EP by binding to human pulmonary surfactant, resulting in its accumulation in the alveolar spaces in concentrations high enough to injure the epithelium and cause inflammation.

Philit et al.[9] defined acute EP based on the following criteria: (i) febrile illness of less than 5 days' duration; (ii) diffuse bilateral pulmonary infiltrates; (iii) hypoxaemia (partial pressure of oxygen of less than 60 mmHg or pulse oximetry reading of <90% on room air); and (iv) BAL with greater than 25% eosinophils or EP at lung biopsy. Solomon and Schwarz[12] have postulated that a definitive diagnosis of drug- or toxin-induced EP could be made in patients who have (i) exposure to a suspected drug or toxin in the appropriate time frame; (ii) no other cause of eosinophilic

Table IV. EBGM, EB05 and EB95 values for the nine antimicrobial agents listed in figure 1 as having been reported with the MedDRA® preferred term of 'Eosinophilic Pneumonia' in Adverse Event Reporting System reports (sorted by descending EBGM value)[a]

Generic name	N	EBGM	EB05	EB95
Daptomycin	23	80.5	56.2	112.4
Cefpirome	4	63.1	17.6	154.5
Pyrimethamine and sulfadoxine	7	33.8	15.6	63.7
Nitrofurantoin	40	22.1	16.9	28.5
Minocycline	32	13.0	8.9	17.8
Meropenem	7	7.9	3.0	24.9
Clarithromycin	27	6.5	4.6	9.2
Dapsone	5	5.9	2.1	26.6
Azithromycin	17	4.6	3.1	6.8

a Only the daptomycin reports were reviewed for potential causality and duplicate submission.

EB05 and EB95 = lower and upper 90% confidence intervals for the EBGM, respectively; **EBGM** = Empirical Bayes Geometric Mean; **MedDRA®** = Medical Dictionary for Regulatory Activities; **N** = number of Adverse Event Reporting System reports with Eosinophilic Pneumonia.

pulmonary infiltrates (e.g. fungal or parasitic pneumonia); (iii) clinical improvement after cessation of the suspected drug or toxin; and (iv) recurrence of symptoms with rechallenge to the suspected drug or toxin. Given the hazards, rechallenging patients is generally not recommended.

We developed our case definition for 'definite' EP (see table I) prior to our review of the cases. Our definition was generally consistent with the published literature;[9-15] however, patients with lung biopsies considered consistent with EP but not meeting the BAL eosinophilia criterion were not considered 'definite' cases, mainly because we did not originally anticipate the availability of lung biopsy results from AERS reports. Five patients who did not meet all the criteria for a 'definite' case had lung biopsy results that appeared to be consistent with EP. While it is likely that these and several other 'probable' and 'possible' cases also had acute EP due to daptomycin, we only included as 'definite' the cases that met all of the predefined criteria because we felt that such patients would provide the strongest evidence for a potential association between EP and daptomycin use.

It is notable that three patients (two definite and one probable) had recurrence of signs/symptoms, including fever, dyspnoea and hypoxaemia, with daptomycin rechallenge. This evidence would strongly suggest biological plausibility between treatment with daptomycin and the development of EP.

The fulminant nature of the seven definite cases suggests that all were cases of acute EP. All improved rapidly after daptomycin was withdrawn, i.e. experienced a positive dechallenge. Systemic corticosteroids were initiated in the majority of cases. However, as noted by Lal and Assimacopoulos[2] some EP patients may develop a chronic pneumonitis and require long-term corticosteroid therapy.

Our study has the following limitations. As a consequence of spontaneous reporting, the analysis of the AERS data is limited by underreporting, lack of randomization, detection and reporting biases and missing data. Specifically, the AERS reports frequently lacked information on pertinent criteria for inclusion as 'definite' cases, such as eosinophil counts on BALs or inclusion of a history of fever. The variable quality of reporting and missing data likely contributed to an underestimate of the actual number of definite cases. The seventh definite case (see table II) exemplifies how inadequate information can lead to misclassification. Additional information found in the published case report[18] allowed for classifying the patient as a definite case of EP associated with daptomycin exposure. Confounding from concomitant medications and/or concurrent illnesses may also hamper causality assessments.

In order to allow for time to analyse the data and develop the manuscript, we made an arbitrary decision to use October 2010 as the cut-off date for additional case finding. However, we continue to monitor to assess for trends with this important safety signal.

Data mining revealed high EBGM and EB05 values for the daptomycin-EP pair based on an analysis of all AEs for all drugs in the FDA AERS database. We also noted elevated EBGM and EB05 values for other antimicrobial agents. As such, the data mining indicates that EP as an AE may not be uniquely associated with daptomycin but could also be observed with other antimicrobial agents. We are currently further investigating the associations between these agents and EP. As previously noted, the higher the EBGM value for a particular drug-AE combination, the higher the reporting association between that drug and AE in the data. However, the reader is reminded that AERS contains spontaneously submitted data on AEs by the public. Reporting biases such as under- and over-reporting of drug events can occur in AERS. Because of the spontaneous nature of reporting, the results of this analysis should not be interpreted as a formal comparison of treatment groups or of their relative risks. The effects of concomitant illnesses or therapy among the cases in AERS cannot be fully controlled in this data mining analysis. Other factors such as the length of time of marketing, drug usage, changes in coding practices over time, and relevant clinical and preclinical data should also be considered when interpreting these data mining results. Additionally, we note that the high EBGM value for the PT of 'Eosinophilic Pneumonia' among daptomycin-treated patients could have, in part, been related to stimulated

reporting after our safety communication, which was posted on 29 July 2010 (and the revised labelling, which the company posted on 13 August 2010). However, the overall trend of highly disproportionate reporting for the PT of 'Eosinophilic Pneumonia' among daptomycin-treated patients has remained consistent over time.

Given the limitations inherent in the AERS data as previously described, the high scores do not prove causality or an increased relative risk of the drug-AE in all patients exposed to daptomycin. That said, the case reports complemented the data mining analysis and provided compelling evidence, e.g. the dechallenge and rechallenge cases, of biological plausibility between treatment with daptomycin and the development of EP.

The drug utilization data suggest a progressive increase in the utilization of daptomycin since 2004; hence, it is likely that more cases of daptomycin-associated EP will be observed. Recognition of the early manifestations of EP will be key. Therefore, it is prudent that healthcare providers include EP in their differential diagnosis when daptomycin-treated patients develop new fever, dyspnoea with hypoxaemia or pulmonary infiltrates during therapy.

Conclusions

We identified 7 definite, 13 probable and 38 possible cases of EP associated with daptomycin administration. These cases provide evidence of a temporal association between daptomycin exposure and the subsequent development of EP. Biological plausibility is strengthened by the positive dechallenge and rechallenge cases. As AERS is based on voluntary reporting, the true incidence of EP due to daptomycin cannot be assessed. Daptomycin-induced EP can lead to acute respiratory failure if not recognized readily and managed appropriately. Healthcare providers should have a heightened awareness of this serious AE associated with daptomycin use.

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The views expressed in this report are those of the authors and do not necessarily represent the views of the US FDA.

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