Overcoming and containing bacterial resistance: appropriate antibiotic use in community-acquired RTIs

Stephen Brunton
4315 Physicians Blvd, Suite 101, Harrisburg, NC 28075, USA
Tel.: +1 704 455 6527
Fax: +1 704 455 2146
ozdoc@aol.com

The global spread of antibiotic resistance is driving the need for more thoughtful antibiotic prescribing. This paper reviews the principles of appropriate antibiotic therapy for community-acquired respiratory tract infections. Appropriate therapy options include: prescribing antibiotics only when they are beneficial to the patient; using agents that target the likely pathogens, taking into account local resistance patterns and risk factors for infection by resistant pathogens while not affecting the bowel flora and other nonrespiratory organisms; and using a dosing schedule and treatment duration that optimizes efficacy, tolerability and adherence to treatment.

The spread of antibiotic resistance among bacteria responsible for common infections has prompted calls for improved use of antibiotics in the USA and elsewhere [1,2]. Community-acquired respiratory tract infections (RTIs), such as acute bacterial sinusitis (ABS), acute exacerbations of chronic bronchitis (AECB), and community-acquired pneumonia (CAP), account for the majority of antibiotic prescriptions in outpatients [3].

The widespread and unnecessary use of antibiotics for viral RTIs contributes substantially to the selective pressure driving resistance [4]. Educational campaigns have had some success in reducing total antibiotic use in this setting [3]. However, in the absence of diagnostic tests the differentiation of viral and bacterial infections based on clinical signs and symptoms remains a major challenge [5]. A number of guidelines have sought to encourage better discrimination of viral from bacterial infections [6–8]. These generally recommend that acute RTIs among patients with no comorbidities or other predisposing factors are unlikely to be bacterial in origin for infections of short duration. Antibiotics are of no benefit for RTIs caused by viruses. They should thus be reserved for infections of more than 7 days' duration, which are more likely to be bacterial in origin, and for patients with specific risk factors for bacterial infection [5].

The spread of antibiotic resistance among bacteria responsible for common infections has prompted calls for improved use of antibiotics in the USA and elsewhere [1,2]. Frequently, the emphasis has been on reducing the amount of antibiotics prescribed, but there is a potential drawback to this approach, which is highlighted by the excess mortality that may occur [9]. This emphasizes the need to accurately identify patients with bacterial rather than viral RTIs.

Attention must now shift towards improving antibiotic prescribing for bacterial RTIs, with regard to the quality rather than merely the quantity of antibiotics used [10–12]. According to the CDC, appropriate antibiotic use aims to maximize therapeutic impact while minimizing toxicity and the development of resistance [13]. This involves the selection of the most appropriate antibiotic, dose and treatment duration, in addition to promoting adherence to therapy (e.g., by educating patients and using antibiotics with more convenient and simpler dosing regimens). In outlining these aspects of therapy, this paper reviews the concepts behind appropriate prescribing for community-acquired RTIs of bacterial origin and how these concepts can overcome and help to contain antibiotic resistance in this setting. In practice, different countries recommend different antibiotics for similar situations in their guidelines [14–16]. These guidelines differ in their use of evidence and expert consensus and must also take account of the local patterns of antibiotic resistance.

Spectrum of activity

A causative organism is rarely isolated before antibiotic treatment for community-acquired RTIs is begun. Hence, antibiotics for community-acquired RTIs are usually chosen empirically according to the likely causative pathogens and their antibiotic susceptibilities. The organisms most commonly responsible for community-acquired RTIs of bacterial origin are *Streptococcus pneumoniae* (the 'pneumococcus'), *Haemophilus influenzae* and *Moraxella catarrhalis* (**Table 1**). Atypical and intracellular organisms, such as *Chlamydophila (*previously *Chlamydia) pneumoniae*, *Legionella pneumophila* and *Mycoplasma*

Keywords: antibiotics, bacterial, bronchitis, drug resistance, pneumonia, respiratory tract infections, sinusitis

Future Drugs Ltd

Table 1. Bacterial pathogens responsible for the most common community-acquired respiratory tract infections in the USA.

Pathogen	CAP (%)	AECB (%)	ABS (%)
Typical pathogens			
Streptococcus pneumoniae	20–60	15–25	34
Haemophilus influenzae	3–10	30–59	35
Moraxella catarrhalis	2	3–22	0–8
Atypical/intracellular pathogens			
Legionella spp.	2–8	NA	NA
Chlamydophila pneumoniae	4–6	NA	NA
Mycoplasma pneumoniae	1–6	NA	NA

ABS: Acute bacterial sinusitis; AECB: Acute exacerbations of chronic bronchitis; CAP: Community-acquired pneumonia; NA: Not available.
Adapted from [44].

pneumoniae, are also potential causes of CAP and, according to recommendations by the Infectious Diseases Society of America, should be covered by empirical therapy [17]. These atypical organisms are also implicated in a minority (<10%) of AECB cases [18].

Antibiotics for the empirical treatment of community-acquired RTIs should have a targeted spectrum of activity covering implicated pathogens, without unnecessary broad-spectrum effects on bowel flora and other organisms. If a causative organism is identified, then it is possible to choose antibiotics with even greater specificity. Agents available for use in the treatment of RTIs and currently recommended in treatment guidelines [14–16] include β-lactams (e.g., amoxicillin, cefuroxime), β-lactam/β-lacatamase inhibitor combinations (e.g., amoxicillin–clavulanate), macrolides/azalides (e.g., erythromycin, azithromycin), doxycycline, trimethoprim–sulfamethoxazole, respiratory fluoroquinolones (e.g., levofloxacin, moxifloxacin) and ketolides (e.g., telithromycin). Typically, β-lactams, macrolides/azalides and doxycycline are recommended as first-line agents with newer drugs, such as ketolides and fluoroquinolones, reserved for patients with more severe disease and those who have experienced treatment failure with first-line agents. The new agent, linezolid, has a spectrum of activity limited to Gram-positive organisms and is not recommended for empirical treatment of ambulatory patients [19].

Resistance

Resistance patterns

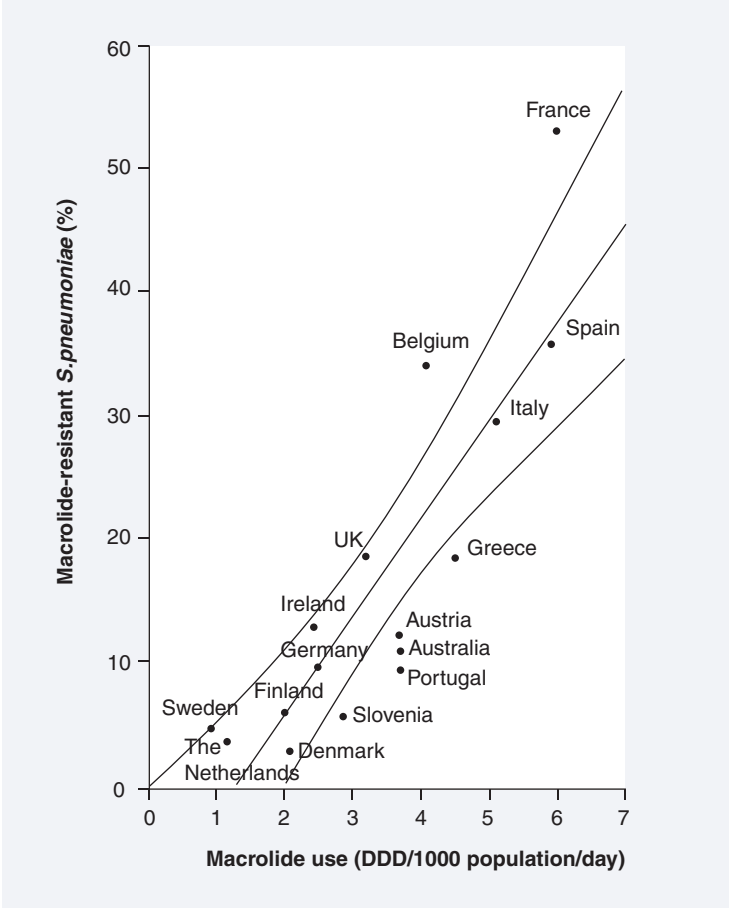
S. pneumoniae – a primary bacterial cause of ABS [20], AECB [18] and CAP [17] – is commonly resistant *in vitro* to β-lactams, macrolides, trimethoprim–sulfamethoxazole and tetracyclines. A number of studies (including the Alexander project [21], the SENTRY [22] and TRUST [23] antimicrobial surveillance programs) demonstrate that antibiotic resistance rates have tended to increase over time. The most recent data from the ongoing Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) US study show that, among 31,001 *S. pneumoniae* isolates collected between 2000 and 2003, 29.4% were resistant to erythromycin and 22.5% to penicillin [24]. The prevalence of macrolide resistance was also found to differ between US states, with the highest rate (48.2%) reported in Louisiana (LA, USA) and the lowest rate (15.2%) reported in Vermont (VT, Canada) in the period 2001–2002 [25]. This suggests that a switch away from macrolides as first-line agents may be justified in states with high rates of macrolide resistance and physicians should be aware of local antibiotic resistance surveillance data.

A particular concern is the rise in prevalence of multiple antibacterial drug-resistant *S. pneumoniae* strains. Approximately 31% of *S. pneumoniae* isolates collected in the PROTEKT US study between 2000 and 2003 were resistant to two or more antibiotic classes [24]. Macrolide resistance in the USA is most commonly associated with the *mef*(A) genotype, but isolates with the dual *erm*(B) + *mef*(A) genotype, which confers high-level macrolide resistance and multidrug resistance, are becoming more common [25].

The 'respiratory' fluoroquinolones and telithromycin remain reliably active against *S. pneumoniae*. Fluoroquinolone resistance in *S. pneumoniae* remains rare, with a prevalence of approximately 1% [24,26]. However, the trend in fluoroquinolone resistance in the USA has been towards increasing resistance over time [26] and this trend is expected to continue [27]. Infection with a fluoroquinolone-resistant isolate is more likely in nosocomial infections and infections acquired in residential care homes compared with isolates active in the general community [28]. *S. pneumoniae* isolates with low-level resistance to telithromycin have been reported [29] but US resistance surveillance data suggest that *in vitro* telithromycin resistance among *S. pneumoniae* remains very low (<0.8%) [30].

The other major pathogens implicated in community-acquired RTIs, *H. influenzae* and *M. catarrhalis*, commonly produce β-lactamase enzymes that inactivate many β-lactam agents, including penicillin, amoxicillin and some early

Figure 1. Relationship between macrolide use in the outpatient setting and prevalence of macrolide-resistant *Streptococcus pneumoniae* in 16 industrialized countries.



A regression line was fitted with 95% confidence intervals ($r = 0.88$; $p < 0.001$). DDD: defined daily dose. Adapted from [50].

cephalosporins. In the USA, 28% of *H. influenzae* isolates and over 90% of *M. catarrhalis* isolates produce β-lactamases [30,31]. Agents with undiminished activity against β-lactamase-positive strains include amoxicillin–clavulanate, azithromycin, fluoroquinolones and telithromycin [30,31].

Impact of resistance

In the USA, macrolides/azalides are favored as the first-line agents in treating RTIs. Macrolides are effective against typical RTI pathogens and, in contrast to β-lactams, are also effective against atypical/intracellular pathogens [32] and β-lactamase-producing Gram-negative organisms [33]. The primary macrolide resistance mechanism observed in the USA (*mef*[A]) confers intermediate *in vitro* resistance compared with Europe where the *erm*(B) mechanism confers higher-level resistance [25] and where the use of β-lactams as first-line agents is more common. However, the spread of higher macrolide resistance clones in the USA may require a re-evaluation [14] or limitation [34] of the use of macrolides.

Bacteriologic eradication is the main determinant of clinical outcome in the treatment of community-acquired RTIs [35]. Surprisingly, the effect on clinical outcomes of infection by *in vitro* antibiotic-resistant strains is poorly characterized. Small studies and case reports support a link between macrolide resistance and treatment failure in CAP and bacteremia [34–37] and have led some experts to suggest that the impact of macrolide-resistant *S. pneumoniae* may be underestimated [38]. The concern about increasing prevalence of macrolide resistance in *S. pneumoniae* may explain the shift in prescribing in the USA towards fluoroquinolones in the treatment of CAP [39]. This trend is worrying, since the guidelines reserving fluoroquinolone use for higher-risk patients do not appear to be being followed [39] and there are documented case reports of fluoroquinolone treatment failures among patients with CAP caused by fluoroquinolone-resistant *S. pneumoniae* [40–42].

Antibiotic resistance has the potential to increase the healthcare and socioeconomic costs associated with infections [43]. In hospitalized patients, antibiotic-resistant infections have been associated with increased healthcare utilization in terms of duration of hospitalization, antibiotic drug costs and nursing charges [44,45]. Further research is needed in order to better define and quantify the burden of resistance in the outpatient setting [46].

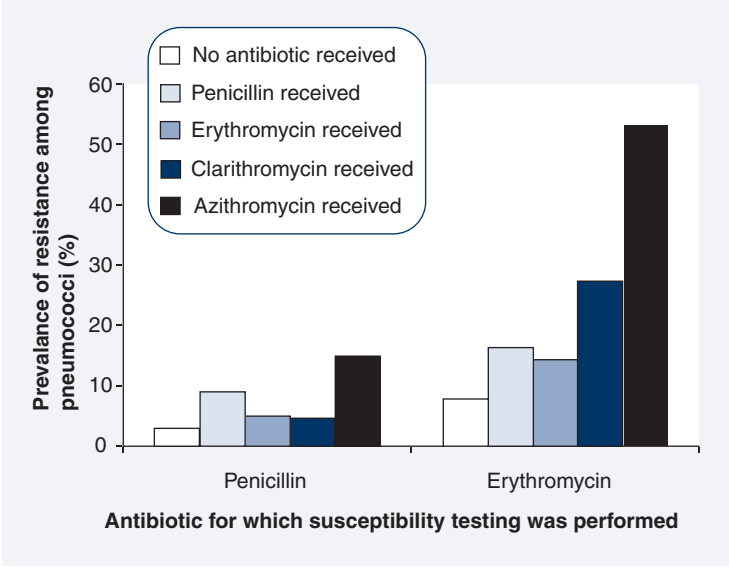
Selection & induction of resistance

Antibiotic consumption in the community is linked with bacterial-resistance patterns through complex relationships [47], thus the propensity for different antibiotic regimens to select for or induce resistance is a factor to be considered when choosing therapy.

Resistance at the population level

Ecological studies have demonstrated a correlation between β-lactam and macrolide consumption at the population level with high levels of pneumococcal resistance to these agents [48–52]. For example, Albrich and collegues correlated macrolide use with resistance levels in 16 European countries (**Figure 1**) [50]. Data suggest that it is macrolides and not β-lactams that are

Figure 2. Association between the use of antibiotics during the 3-month period before invasive pneumococcal infection and the susceptibility of the infecting isolate to penicillin or erythromycin.



Adapted from [28].

the main agents promoting both penicillin and macrolide resistance [49]. Recent studies have implicated the increased use of once-daily macrolides (e.g., azithromycin) as the principal driver of macrolide resistance [49,51,52]. The prolonged half-life of azithromycin is suggested to result in subinhibitory tissue concentrations that favor the selection of resistant strains [52].

Increased use of levofloxacin in the USA has also been correlated with so far modest increases in fluoroquinolone resistance in *S. pneumoniae* [53]. However, the rise of fluoroquinolone use in the community has been associated with increased levels of resistance in Gram-negative organisms, such as *Pseudomonas aeruginosa* and Enterobacteriaceae, which can cause serious infections in hospitalized patients [54,55]. In contrast, telithromycin appears to have a lower ecological impact on gastrointestinal flora than other agents [56].

According to the CDC, the widespread use of azithromycin, clarithromycin and fluoroquinolones in the USA warrants concern in light of resistance trends that threaten the utility of these agents in hospitalized patients [11].

Predicting resistance in individuals

At the level of the individual patient, previous antibiotic use is predictive of infection by a resistant organism, as demonstrated by a prospective Canadian study involving 3339 patients with invasive pneumococcal infections [28]. Upon multivariate analysis, use of clarithromycin or azithromycin in the previous 3 months was significantly associated with infection by a macrolide-resistant strain, with odds ratios (ORs) of 3.93 (95% confidence interval [CI]: 2.16–7.16; $p < 0.001$) and 9.93 (95% CI: 4.85–20.3; $p < 0.001$) for these two agents, respectively (**Figure 2**). Previous azithromycin use was also significantly associated with resistance to penicillin and trimethoprim–sulfamethoxazole, while fluoroquinolone use predicted fluoroquinolone resistance with an OR = 12 ($p < 0.001$). Fluoroquinolone use within the previous month is also predictive for the emergence of resistant Gram-negative bacilli in the gastrointestinal flora [57].

Factors affecting the increase of resistance

Bactericidal agents (e.g., penicillins, fluoroquinolones and ketolides) may be less likely to select resistant strains than bacteriostatic agents (e.g., macrolides) owing to more rapid eradication of organisms by the former [58]. Resistance selection may be more likely when bacteria are exposed to prolonged, subtherapeutic antibiotic concentrations. This not only explains the aforementioned resistance selection by azithromycin, but also why β-lactams administered at low daily doses for long treatment durations (>5 days) are associated with an increased risk of nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* as compared with high-dose, short-course regimens [59,60]. This highlights the need to prescribe antibiotics at appropriate doses based on pharmacokinetic/pharmacodynamic principles [14]. High-dose amoxicillin courses have thus been developed to combat the increase in penicillin resistance among *S. pneumoniae* strains [61].

Certain antibiotics may have inherent characteristics that reduce their propensity to induce or select for resistance. For example, ketolides, unlike macrolides, do not induce the macrolide–lincosamide–streptogramin$_B$ resistance phenotype coded for by the *erm*(B) genotype [57,62] and the activity of telithromycin has not changed between 1999 and 2003, including in those countries where this antibiotic is in clinical use [63]. Similarly, respiratory fluoroquinolone resistance in *S. pneumoniae* has remained at approximately 1% in the USA [24,26]. This is because resistance selection mainly occurs via a stepwise mechanism, with mutations required in both the topoisomerase IV and gyrase genes. Relatively often strains have mutations in one gene but not both [64].

Highlights

- The spread of antibiotic resistance requires improved use of antibiotics in clinical practice.
- Inappropriate use of antibiotics in viral infections helps drive resistance, but differentiation of viral and bacterial respiratory tract illness remains a major challenge.
- Antibiotic-resistant infections are associated with increased healthcare utilization and increased costs.
- Empiric antibiotic treatment of community-acquired respiratory tract infections (RTIs) must be effective against all of the likely causes of the infection – *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and also 'atypical' organisms, such as *Chlamydophila pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae*.
- Antibiotic resistance surveillance studies are providing vital local resistance data that can inform local antibiotic prescribing.
- Previous antibiotic use by a patient is predictive of infection by a resistant organism.
- Drug treatment regimens and course duration are important considerations in determining patient adherence to antibacterial treatment. Poor adherence to treatment can expose bacteria to subtherapeutic drug levels, leading to treatment failure and resistance selection.

Adherence & tolerability

According to a recent meta-analysis, mean adherence to antibiotic dosing regimens may be as low as 62% [65]. Poor adherence to antibiotic regimens can expose bacteria to subtherapeutic doses, and hence may lead to treatment failure and resistance selection. Patients are more likely to comply with dosing regimens that are short and conveniently administered, preferably once daily [66]. Short-course therapy is of direct benefit in reducing the selective pressure for resistance [60,61] and a growing body of evidence supports its use in community-acquired RTIs [67]. However, once-daily administration must be coupled with an appropriate pharmacokinetic/pharmacodynamic profile in order to avoid subtherapeutic concentrations and the associated risk of resistance selection.

Tolerability also has an important influence on compliance, as adverse events may prompt patients to discontinue therapy [66]. Thus, physicians must consider the relative tolerability of different antibiotics in the relevant patient population when selecting therapy for community-acquired RTIs. The use of shorter treatment courses may also contribute to reducing the risk of adverse events.

Expert commentary

The association between antibiotic use and widespread bacterial resistance in pathogens responsible for community-acquired RTIs underscores the importance of selecting appropriate antibiotic therapy that maximizes clinical outcomes and cost-effectiveness, while limiting the selective pressure for resistance.

Agents with appropriate antibacterial spectra, documented efficacy, good tolerability, a low potential for resistance induction, and a convenient dosing regimen will best meet this need.

Outlook

Ongoing antibacterial resistance surveillance studies suggest that, despite an increasing awareness of the problems of antibiotic resistance, β-lactam and macrolide nonsusceptibility will remain significant problems for the treatment of community-acquired RTIs in the foreseeable future. At a time when there is increasing pressure on healthcare provision services to contain costs, the expense of increased morbidity or mortality resulting from treatment failure with older, established antibiotics will have to be balanced against the costs of newer, more effective antibiotic drugs. Some of the information required for these decisions will be the increased provision of accurate, localized antibacterial surveillance data. The introduction of new antimicrobials will have an impact, but newer agents are likely to be in the same classes as existing drugs, underlining the need for appropriate prescribing now.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Interagency Task Force on Antimicrobial Resistance. *Public health action plan to combat antimicrobial resistance.* Centers for Disease Control and Prevention, GA, USA (2001).
2. World Health Organization. *WHO global strategy for the containment of antimicrobial resistance.* World Health Organization, Geneva, Switzerland (2001).
3. McCaig LF, Besser RE, Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. *JAMA* 287, 3096–3102 (2002).
4. Stone S, Gonzales R, Maselli J, Lowenstein SR. Antibiotic prescribing for patients with colds, upper respiratory tract infections, and bronchitis: a national study of hospital-based emergency departments. *Ann. Emerg. Med.* 36, 320–327 (2000).
5. Brunton S. Treating community-acquired bacterial respiratory tract infections: update on etiology, diagnosis, and antimicrobial therapy. *J. Fam. Pract.* 54, 357–364 (2005).
6. Dowell SF, Marcy SM, Phillips WR, Gerber MA, Schwartz B. Principles of judicious use of antimicrobial agents for pediatric upper respiratory tract infections. *Pediatrics* 101(Suppl.), 163–165 (1998).
7. Gonzales R, Bartlett JG, Besser RE *et al.* Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific

aims, and methods. *Ann. Intern. Med.* 134, 479–486 (2001).

8. Irwin RS, Baumann MH, Bolser DC *et al.* for the American College of Chest Physicians (ACCP). Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 129(1 Suppl.), 1S–23S (2006).
9. Price DB, Honeybourne D, Little P *et al.* Community-acquired pneumonia mortality. a potential link to antibiotic prescribing trends in general practice. *Respir Med.* 91, 17–24 (2004).
10. Ball P, Baquero F, Cars O *et al.* Antibiotic therapy of community respiratory tract infections: strategies for optimal outcomes and minimized resistance emergence. *J. Antimicrob. Chemother.* 49, 31–40 (2002).
11. McCaig LF, Besser RE, Hughes JM. Antimicrobial drug prescriptions in ambulatory care settings, United States, 1992–2000. *Emerg. Infect. Dis.* 9, 432–437 (2003).
12. Slama TG, Amin A, Brunton SA *et al.* A clinician's guide to the appropriate and accurate use of antibiotics: the council for appropriate and rational antibiotic therapy. *Am. J. Med.* 118 (Suppl. 7A), 1S–6S (2005).

• **Useful guide highlighting the need for appropriate antibiotic prescribing.**

13. Bell DM. Promoting appropriate antimicrobial drug use: perspective from the Centers for Disease Control and Prevention. *Clin. Infect. Dis.* 33(Suppl. 3), 245–250 (2001).
14. File TM Jr, Garau J, Blasi F *et al.* Guidelines for empiric antimicrobial prescribing in community-acquired pneumonia. *Chest* 125, 1888–1901 (2004).
15. Blasi F, Ewig S, Torres A, Huchon G. A review of guidelines for antibacterial use in acute exacerbations of chronic bronchitis. *Pulm. Pharmacol. Ther.* 19, 361–369 (2006).
16. Klossek JM, Federspil P. Update on treatment guidelines for acute bacterial sinusitis. *Int. J. Clin. Pract.* 59, 230–238 (2005).
17. Mandell LA, Bartlett JG, Dowell SF, File TM, Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin. Infect. Dis.* 37, 1405–1433 (2003).

• **Current guidelines for antibiotic prescribing produced by the Infectious Diseases Society of America with specific recommendations in tabulated format.**

18. Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. *Chest* 117(5 Suppl. 2), 380S–385S (2000).
19. Wilcox MH. Efficacy of linezolid versus comparator therapies in Gram-positive infections. *J. Antimicrob. Chemother.* 51(Suppl. 2), ii27–ii35 (2003).
20. Anon JB, Jacobs MR, Poole MD *et al.* Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol. Head Neck Surg.* 130(1 Suppl.), 1–45 (2004).

• **Update of the Sinus and Allergy Health Partnership review of bacterial sinusitis combined with antibiotic therapy guidelines for adult and pediatric patients.**

21. Felmingham D, White AR, Jacobs MR *et al.* The Alexander Project: the benefits from a decade of surveillance. *J. Antimicrob. Chemother.* 56(Suppl. 2), ii3–ii21 (2005).
22. Pfaller MA, Jones RN, Doern GV, Kugler K. Bacterial pathogens isolated from patients with bloodstream infection: frequencies of occurrence and antimicrobial susceptibility patterns from the SENTRY antimicrobial surveillance program (United States and Canada, 1997). *Antimicrob. Agents Chemother.* 42, 1762–1770 (1998).
23. Sahm DF. Resistance issues and community-acquired respiratory infections. *Clin. Cornerstone* (Suppl. 3), S4–S11 (2003).
24. Farrell DJ, Jenkins SG. Distribution across the USA of macrolide resistance and macrolide resistance mechanisms among *Streptococcus pneumoniae* isolates collected from patients with respiratory tract infections: PROTEKT US 2001–2002. *J. Antimicrob. Chemother.* 54(Suppl. 1), i17–i22 (2004).
25. Jenkins SG, Farrell DJ, Patel M, Lavin BS. Trends in anti-bacterial resistance among *Streptococcus pneumoniae* isolated in the USA, 2002–2003: PROTEKT US years 1–3. *J. Infect.* 51, 355–363 (2005).
26. Pletz MWR, McGee L, Jorgensen J *et al.* Levofloxacin-resistant invasive *Streptococcus pneumoniae* in the United States: evidence for clonal spread and the impact of conjugate pneumococcal vaccine. *Antimicrob. Agents Chemother*. 48, 3491–3497 (2004).
27. Linder JA, Huang ES, Steinman MA *et al.* Fluoroquinolone prescribing in the United States: 1995 to 2002. *Am. J. Med.* 118, 259–268 (2005).
28. Vanderkooi OG, Low DE, Green K *et al.* Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin. Infect. Dis.* 40, 1288–1297 (2005).

•• **Describes factors likely to predispose individuals to infection by antibiotic-resistant *S. pneumoniae*.**

29. Rantala M, Haanpera-Heikkinen M, Lindgren M, Seppala H, Huovinen P, Jalava J. *Streptococcus pneumoniae* isolates resistant to telithromycin. *Antimicrob. Agents Chemother.* 50, 1855–1858 (2006).
30. Brown SD, Rybak MJ. Antimicrobial susceptibility of *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* collected from patients across the USA, in 2001–2002, as part of the PROTEKT US study. *J. Antimicrob. Chemother.* 54(Suppl. 1), i7–i15 (2004).
31. Hoban D, Felmingham D. The PROTEKT surveillance study: antimicrobial susceptibility of *Haemophilus influenzae* and *Moraxella catarrhalis* from community-acquired respiratory tract infection. *J. Antimicrob. Chemother.* 50(Suppl. S1), 49–59 (2002).
32. Dagan R, Klugman KP, Craig WA, Baquero F. Evidence to support the rationale that bacterial eradication in respiratory tract infection is an important aim of antimicrobial therapy. *J. Antimicrob. Chemother.* 47, 129–140 (2001).
33. Metlay JP, Singer DE. Outcomes in lower respiratory tract infections and the impact of antimicrobial drug resistance. *Clin. Microbiol. Infect.* 8(Suppl. 2), 1–11 (2002).
34. Kelley MA, Weber DJ, Gilligan P *et al.* . Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. *Clin. Infect. Dis.* 31, 1008–1011 (2000).
35. Waterer GW, Wunderink RG, Jones CB. Fatal pneumococcal pneumonia attributed to macrolide resistance and azithromycin monotherapy. *Chest* 118, 1839–1840 (2000).
36. Fogarty C, Goldschmidt R, Bush K. Bacteremic pneumonia due to multidrug-resistant pneumococci in 3 patients treated unsuccessfully with azithromycin and successfully with levofloxacin. *Clin. Infect. Dis.* 31, 613–615 (2000).
37. Lonks JR, Garau J, Gomez L *et al.* Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. *Clin. Infect. Dis*. 35, 556–564 (2002).

•• **Describes treatment failures caused by macrolide-resistant pneumococci, which provides important clinical evidence for the problems of antibiotic resistance in the treatment of respiratory tract infections.**

38. Klugman KP, Lonks JR. Hidden epidemic of macrolide-resistant pneumococci. *Emerg. Infect. Dis.* 11, 802–807 (2005).

39. MacDougall C, Guglielmo BJ, Maselli J, Gonzales R. Antimicrobial drug prescribing for pneumonia in ambulatory care. *Emerg. Infect. Dis.* 11, 380–384 (2005).
40. Davidson R, Cavalcanti R, Brunton JL *et al*. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. *N. Engl. J. Med.* 346, 747–750 (2002).
41. Endimiani A, Brigante G, Bettaccini AA, Luzzaro F, Grossi P, Toniolo AQ. Failure of levofloxacin treatment in community-acquired pneumococcal pneumonia. *BMC Infect. Dis.* 5, 106 (2005).
42. Fuller JD, Low DE. A review of *Streptococcus pneumoniae* infection treatment failures associated with fluoroquinolone resistance. *Clin. Infect. Dis.* 41, 118–121 (2005).
43. McGowan JE. The economic impact of antimicrobial resistance. *Emerg. Infect. Dis.* 7, 286–292 (2001).
44. Nicolau D. Clinical and economic implications of antimicrobial resistance for the management of community-acquired respiratory tract infections. *J. Antimicrob. Chemother.* 50(Suppl. S1), 61–70 (2002).
45. Klepser ME, Klepser DG, Ernst EJ *et al*. Health care resource utilization associated with treatment of penicillin-susceptible and -nonsusceptible isolates of *Streptococcus pneumoniae*. *Pharmacotherapy* 23, 349–359 (2003).
46. Howard DH, Scott RD. The economic burden of drug resistance. *Clin. Infect. Dis.* 41(Suppl. 4), S283–S286 (2005).
47. Baquero F, Baquero-Artigao G, Cantón R, García-Rey C. Antibiotic consumption and resistance selection in *Streptococcus pneumoniae*. *J. Antimicrob. Chemother.* 50(Suppl. S2), 27–37 (2002).
48. Granizo JJ, Aguilar L, Casal J, Garcia-Rey C, Dal-Re R, Baquero F. *Streptococcus pneumoniae* resistance to erythromycin and penicillin in relation to macrolide and β-lactam consumption in Spain (1979–1997). *J. Antimicrob. Chemother.* 46, 767–773 (2000).
49. Garciá-Rey C, Aguilar L, Baquero F, Casal J, Dal-Re R. Importance of local variations in antibiotic consumption and geographical differences of erythromycin and penicillin resistance in *Streptococcus pneumoniae*. *J. Clin. Microbiol.* 40, 159–164 (2002).
50. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerg. Infect. Dis.* 10, 514–517 (2004).
51. Dias R, Caniça M. Emergence of invasive erythromycin-resistant *Streptococcus pneumoniae* strains in Portugal: contribution and phylogenetic relatedness of serotype 14. *J. Antimicrob. Chemother.* 54, 1035–1039 (2004).
52. Barkai G, Greenberg D, Givon-Lavi N, Dreifuss E, Vardy D, Dagan R. Community prescribing and resistant *Streptococcus pneumoniae*. *Emerg. Infect. Dis.* 11, 829–837 (2005).
53. Bhavnani SM, Hammel JP, Jones RN, Ambrose PG. Relationship between increased levofloxacin use and decreased susceptibility of *Streptococcus pneumoniae* in the United States. *Diagn. Microbiol. Infect. Dis.* 51, 31–37 (2005).
54. Polk RE, Johnson CK, McClish D, Wenzel RP, Edmond MB. Predicting hospital rates of fluoroquinolone-resistant *Pseudomonas aeruginosa* from fluoroquinolone use in US hospitals and their surrounding communities. *Clin. Infect. Dis.* 39, 497–503 (2004).
55. MacDougall C, Powell JP, Johnson CK, Edmond MB, Polk RE. Hospital and community fluoroquinolone use and resistance in *Staphylococcus aureus* and *Escherichia coli* in 17 US hospitals. *Clin. Infect. Dis.* 41, 435–440 (2005).
56. Nord CE, Farrell DJ, Leclerq R. Impact of ketolides on resistance selection and ecologic effects during treatment for respiratory tract infections. *Microb. Drug Resist.* 10, 255–263 (2004).
57. Richard P, Delangle MH, Raffi F, Espaze E, Richet H. Impact of fluoroquinolone administration on the emergence of fluoroquinolone-resistant Gram-negative bacilli from gastrointestinal flora. *Clin. Infect. Dis.* 32, 162–166 (2001).
58. Stratton CW. Dead bugs don't mutate. Susceptibility issues in the emergence of bacterial resistance. *Emerg. Infect. Dis.* 9, 10–16 (2003).
59. Guillemot D, Carbon C, Balkau B *et al*. Low dosage and long treatment duration of β-lactam: risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae*. *JAMA* 279, 365–370 (1998).
60. Schrag SJ, Pena C, Fernandez J *et al*. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. *JAMA* 286, 49–56 (2001).
61. Jacobs MR. Building in efficacy: developing solutions to combat drug-resistant S. pneumoniae. *Clin. Microbiol. Infect.* 10(Suppl. 2), 18–27 (2004).
62. Douthwaite S, Champney WS. Structures of ketolides and macrolides determine their mode of interaction with the ribosomal target site. *J. Antimicrob. Chemother.* 48(Suppl. T1), 1–8 (2001).
63. Farrell DJ, Felmingham D. Activities of telithromycin against 13,874 *Streptococcus pneumoniae* isolates collected between 1999 and 2003. *Antimicrob. Agents Chemother.* 48, 1882–1884 (2004).
64. Pan XS, Ambler J, Mehtar S, Fisher LM. Involvement of topoisomerase IV and DNA gyrase as ciprofloxacin targets in *Streptococcus pneumoniae*. *Antimicrob. Agents Chemother.* 40, 2321–2326 (1996).
65. Kardas P, Devine S, Golembesky A, Roberts C. A systematic review and meta-analysis of misuse of antibiotic therapies in the community. *Int. J. Antimicrob. Agents* 26, 106–113 (2005).
66. Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *J. Antimicrob. Chemother.* 49, 897–903 (2002).
    - **Review of data available on adherence to antibiotic treatment regimens and recommendations for improving patient adherence to therapy.**
67. Goff DA. Short-duration therapy for respiratory tract infections. *Ann. Pharmacother.* 38(9 Suppl.), S19–S23 (2004).

Affiliation

Stephen Brunton
4315 Physicians Blvd,
Suite 101, Harrisburg,
NC 28075, USA
Tel.: +1 704 455 6527
Fax: +1 704 455 2146
ozdoc@aol.com

Highlights

- Many strategies have been used to reduce immunogenicity issues with monoclonal antibodies (mAbs), including chimerization, humanization and human mAbs. The development of antibody fragments, such as antigen-binding fragments (Fab′s), is a further advance.
- Fab′s are associated with several benefits compared with whole antibodies including amenability to microbial expression and lack of potential toxicities mediated by the Fc portion of the antibody.
- Certolizumab pegol is a PEGylated, humanized Fab′ fragment of an anti-tumor necrosis factor (TNF)-α mAb.
- PEGylation of the Fab′ fragment is compatible with subcutaneous administration of certolizumab pegol, with potential advantages in terms of convenience and safety.
- The bioavailability after subcutaneous administration is 80–100% and the half-life is approximately 2 weeks.
- Certolizumab pegol has a high affinity and potency for human TNF-α. Preclinical and clinical data have shown the efficacy and tolerability of certolizumab pegol in Crohn′s disease and rheumatoid arthritis.

therapy ('responders') were randomized at week 6 to either certolizumab pegol or placebo. At Week 26, the rates of clinical response (decrease in baseline Crohn's Disease Activity Index [CDAI] score ≥100 points) and remission (CDAI score ≤150 points) irrespective of C-reactive protein levels were significantly higher following treatment with certolizumab pegol compared with placebo. Certolizumab pegol was generally well tolerated, with mild-to-moderate headache being the most commonly reported adverse event [56].

Positive results for a second Phase III trial (PRECiSE 1) have also been presented recently [57]. The primary outcomes were met and the adverse-event profile was in line with that observed in PRECiSE 2.

Collectively, these studies indicate that the Fab′ fragment certolizumab pegol has the potential to be clinically effective, safe and well tolerated for the treatment of CD and RA.

Comparison of certolizumab pegol with other anti-TNF agents

The characteristics of certolizumab pegol, etanercept, adalimumab and infliximab are summarized in **Table 1**.

Expert commentary

Since the inception of targeted antibody technologies in the mid-1960s, immunotherapy has undergone a number of developments in order to improve disease treatment and reduce immunogenicity. Chimeric and humanized mAbs have become important therapeutic and diagnostic tools for a variety of diseases, including CD; however, such antibodies are associated with the production of HACA and HAMA. Antibody Fab′ fragments represent an advance in the field of immunotherapy owing to their small size, flexibility and amenability to rapid production on a large scale.

Certolizumab pegol is a PEGylated humanized Fab′ fragment of an anti-TNF-α mAb. PEGylation ensures a half-life for certolizumab pegol comparable to those of other anti-TNF full IgGs and produces a compound compatible with subcutaneous administration, while humanization of the Fab′ fragment may reduce the potential to cause an immune reaction. Unlike full-length IgG1 antibodies, Fab′ fragments do not mediate ADCC and CDC owing to the absence of an Fc – this may have positive consequences from a safety perspective. Furthermore, Fab′ fragments can also be produced via microbial fermentation – assisting a rapid and reproducible process and a reliable supply.

Certolizumab pegol exhibits high and specific affinity for TNF-α and high *in vitro* potency for TNF-α neutralization. It has also shown efficacy in an animal model of RA, as well as promising efficacy and tolerability results in Phase II and III trials. In comparative *in vitro* studies, the affinity and potency of certolizumab pegol were higher than that observed for the other anti-TNF agents infliximab and adalimumab.

Bibliography

1. Cosimi AB, Colvin RB, Burton RC *et al.* Use of monoclonal antibodies to T-cell subsets for immunologic monitoring and treatment in recipients of renal allografts. *N. Engl. J. Med.* 305, 308–314 (1981).
2. Bach JF, Chatenoud L. Immunologic monitoring of Orthoclone OKT3-treated patients: the problem of antimonoclonal immune response. *Transplant. Proc.* 19, 17–20 (1987).
3. Anderson KC, Bates MP, Slaughenhoupt BL, Pinkus GS, Schlossman SF, Nadler LM. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. *Blood* 63, 1424–1433 (1984).
4. Maloney DG, Grillo-Lopez AJ, Bodkin DJ *et al.* IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin′s lymphoma. *J. Clin. Oncol.* 15, 3266–3274 (1997).

5. Mylotarg™, prescribing information. Wyeth Ayerst, PA, USA (2000).
6. Bross PF, Beitz J, Chen G *et al*. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukaemia. *Clin. Cancer. Res.* 7, 1490–1496 (2001).
7. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 256, 495–497 (1975).
8. Remicade® (infliximab), prescribing information. Schering-Plough Ltd, NJ, USA (2005).
9. Baert F, Norman M, Vermeire S *et al*. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn´s disease. *N. Engl. J. Med.* 348, 601–608 (2003).
10. Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn´s disease: a randomized controlled trial. *Gastroenterology* 124, 917–924 (2003).
11. Lipsky PE, van der Heijde DM, St Clair EW *et al*, and the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N. Engl. J. Med.* 343, 1594–1602 (2000).
12. Wagner CL, Schantz A, Barnathan E *et al*. Consequences of immunogenicity to the therapeutic antibodies ReoPro and Remicade. *Dev. Biol.* 112, 37–53 (2003).
13. Jones PT, Dear PH, Foote J, Neuberger MS, Winter G. Replacing the complementarity-determining regions in a human antibody with those from a mouse. *Nature* 321, 522–525 (1986).
14. Goldsby RA, Kindt TJ, Osborne BA, Kuby J. *Immunology (Fifth Edition).* WH Freeman and Company, NY, USA 128–129 (2003).
15. Adair JR, Athwal DS, Emtage JS. Humanised antibodies. International Patent Publication. WO91/09967 (1991).
16. Riechmann L, Clark M, Waldmann H, Winter G. Reshaping human antibody therapy. *Nature* 332, 323–327 (1988).
17. Campath® (alemtuzumab) prescribing information. Abbott Laboratories, IL, USA (2003).
18. Stephens S, Emtage S, Vetterlein O *et al*. Comprehensive pharmacokinetics of a humanized antibody and analysis of residual anti-idiotypic responses. *Immunology* 85(4), 668–674 (1995).
19. Stack WA, Mann SD, Roy AJ *et al*. Randomised controlled trial of CDP571 antibody to tumour necrosis factor-α in Crohn´s disease. *Lancet* 349, 521–524 (1997).
20. Sandborn WJ, Feagan BG, Radford-Smith G *et al*. CDP571, a humanised monoclonal antibody to tumour necrosis factor α, for moderate to severe Crohn´s disease: a randomised, double blind, placebo controlled trial. *Gut* 53, 1485–1493 (2004).
21. Marks JD, Hoogenboom HR, Bonnert TP, McCafferty J, Griffiths AD, Winter G. By-passing immunization. Human antibodies from V-gene libraries displayed on phage. *J. Mol. Biol.* 222, 581–597 (1991).
22. Humira® (adalimumab) Prescribing information. Abbott Laboratories, IL, USA (2003).
23. Jespers LS, Roberts A, Mahler SM, Winter G, Hoogenboom HR. Guiding the selection of human antibodies from phage display repertoires to a single epitope of an antigen. *Biotechnology (NY)* 12, 899–903 (1994).
24. Sandborn WJ, Hanauer S, Loftus EV Jr *et al*. An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn´s disease. *Am. J. Gastroenterol.* 99, 1984–1989 (2004).
25. Papadakis KA, Shaye OA, Vasiliauskas EA *et al*. Safety and efficacy of adalimumab (D2E7) in Crohn´s disease patients with an attenuated response to infliximab. *Am. J. Gastroenterol.* 100, 75–79 (2005).
26. Hanauer SB, Sandborn WJ, Rutgeerts P *et al*. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn´s disease: the CLASSIC-I trial. *Gastroenterology* 130, 323–333 (2006).
27. Colombel JF, Sandborn WJ, Rutgeerts P *et al*. Adalimumab induces and maintains clinical response and remission in patients with active Crohn´s disease: results of the CHARM trial. *Gastroenterology* 130*(*Suppl. 2), A1–A912 (2006) (Abstract 686d).
28. Weinblatt ME, Keystone EC, Furst DE *et al*. Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 48, 35–45 (2003).
29. van de Putte LB, Atkins C, Malaise M *et al*. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann. Rheum. Dis.* 63, 508–516 (2004).
30. Keystone EC, Kavanaugh AF, Sharp JT *et al*. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomised, placebo-controlled, 52-week trial. *Arthritis Rheum.* 50, 1400–1411 (2004).
31. Clark M. Antibody humanization: a case of the ´Emperor´s new clothes´? *Immunol. Today* 21, 397–402 (2000).
32. Sandborn WJ, Faubion WA. Biologics in inflammatory bowel disease: how much progress have we made? *Gut* 53, 1366–1373 (2004).
33. Fleischmann R, Shealy D. Developing a new generation of TNFα antagonists for the treatment of rheumatoid arthritis. *Mol. Interv.* 3, 310–318 (2003).
34. Nesbitt AM, Henry AJ. High affinity and potency of the PEGylated Fab´ fragment CDP870 – a direct comparison with other anti-TNF agents. *Gut* 53(Suppl. VI), A47 (2004).
35. Van den Brande JM, Braat H, van den Brink GR *et al*. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn´s disease. *Gastroenterology* 124, 1774–1785 (2003).
36. Fossati G, Nesbitt AM. Effet of the anti-TNF agents adalimumab, etanercept, infliximab, and certolizumab pegol (CDP870) on the induction of apoptosis in activated peripheral blood lymphocytes and monocytes. Presented at: the American College of Gastroenterology meeting, Honolulu, Hawaii (2005) (Abstract 512).
37. Lorenz HM, Antoni C, Valerius T *et al*. *In vivo* blockade of TNF α by intravenous infusion of a chimeric monoclonal TNFα antibody in patients with rheumatoid arthritis. *J. Immunol.* 156, 1646–1653 (1996).
38. Myoscint® Prescribing information. Centocor BV, Leiden, The Netherlands (2005).
39. Pastorino F, Brignole C, Marimpietri D *et al*. Doxorubicin-loaded Fab´ fragments of anti-disialoganglioside immunoliposomes selectively inhibit the growth and dissemination of human neuroblastoma in nude mice. *Cancer Res.* 63, 86–92 (2003).
40. Chapman AP, Antoniw P, Spitali M, West S, Stephens S, King DJ. Therapeutic antibody fragments with prolonged *in vivo* half-lives. *Nat. Biotechnol.* 17, 780–783 (1999).
41. Fossati G, Nesbitt AM. *In vitro* complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity by the anti-TNF agents adalimumab, etanercept, infliximab, and certolizumab pegol (CDP870). Presented at: the American College of Gastroenterology meeting, Honolulu, Hawaii (2005) (Abstract 513).

42. Weir AN, Nesbitt A, Chapman AP, Popplewell AG, Antoniw P, Lawson AD. Formatting antibody fragments to mediate specific therapeutic functions. *Biochem. Soc. Trans.* 30, 512–516 (2002).
43. Zalipsky S. Functionalized polyethylene glycol for preparation of biologically relevant conjugates. *Bioconjug. Chem.* 6, 150–165 (1995).
44. Chapman AP. PEGylated antibodies and antibody fragments for improved therapy: a review. *Adv. Drug. Deliv. Rev.* 54, 531–545 (2002).
45. Kitamura K, Takahashi T, Takashina K *et al*. Polyethylene glycol modification of the monoclonal antibody A7 enhances its tumor localization. *Biochem. Biophys. Res. Commun.* 171, 1387–1394 (1990).
46. Leong SR, DeForge L, Presta L *et al*. Adapting pharmacokinetic properties of a humanized anti-interleukin-8 antibody for therapeutic applications using site-specific pegylation. *Cytokine* 16, 106–119 (2001).
47. Wang YS, Youngster S, Grace M, Bausch J, Bordens R, Wyss DF. Structural and biological characterization of pegylated recombinant interferon α-2b and its therapeutic implications. *Adv. Drug. Deliv. Rev.* 53, 547–570 (2002).
48. Foster GR. Pegylated interferon with ribavirin therapy for chronic infection with the hepatitis C virus. *Expert. Opin. Pharmacother.* 4, 685–691 (2003).
49. Baker M, Stringer F, Stephens P. Pharmacokinetic properties of the anti-TNF agent certolizumab pegol. *Ann. Rheum. Dis.* 65(Suppl. II), 175 (2006).
50. Keffer J, Probert L, Cazlaris H *et al*. Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. *EMBO J.* 10, 4025–4031 (1991).
51. Choy EHS, Hazleman B, Smith M *et al*. Efficacy of a novel PEGylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a Phase II double-blinded, randomized, dose-escalating trial. *Rheumatology* 41, 1133–1137 (2002).
52. Moreland LW, Schiff MH, Baumgartner SW *et al*. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann. Intern. Med.* 130, 478–486 (1999).
53. Maini R, St Clair EW, Breedveld F *et al* for the ATTRACT Study Group. Infliximab (chimeric anti-tumour necrosis factor αmonoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 354, 1932–1939 (1999).
54. Schreiber S, Rutgeerts P, Fedorak RN *et al*. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn′s disease. *Gastroenterology* 129, 807–818 (2005).
55. Winter TA, Wright J, Ghosh S, Jahnsen J, Innes A, Round P. Intravenous CDP870, a PEGylated Fab′ fragment of a humanized antitumor necrosis factor antibody, in patients with moderate to severe Crohn′s disease: an exploratory study. *Aliment. Pharmacol. Ther.* 20, 1337–1346 (2004).
56. Schreiber S, Khaliq-Kareemi M, Lawrence I *et al*. Certolizumab pegol, a humanised anti-TNF PEGylated Fab′ fragment, is safe and effective in the maintenance of response and remission following induction in active Crohn′s disease: a Phase III study (PRECiSE 2). *Gut* 54(Suppl. VII), A82 (2005).
57. Sandborn WJ, Feagan BG, Stoinov S *et al*. Certolizumab pegol administered subcutaneously is effective and well tolerated in patients with active Crohn′s disease: results from a 26-week, placebo-controlled Phase III study (PRECiSE 1). *Gastroenterology* 130(Suppl. 2), A1–A912 (2006) (Abstract 745).

Affiliations

Neil Weir
UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE, UK
Tel.: +44 175 353 4655
Fax: +44 175 353 6632
Neil.weir@celltech.UCB-group.com

Dee Athwal
UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE, UK
Tel.: +44 175 353 4655
Fax: +44 175 353 6632

Derek Brown
UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE, UK
Tel.: +44 175 353 4655
Fax: +44 175 353 6632

Roly Foulkes
UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE, UK
Tel.: +44 175 353 4655
Fax: +44 175 353 6632

George Kollias
Institute of Immunology, Biomedical Sciences Research Center, 'Alexander Fleming', Vari, Greece
Tel.: +30 210 965 6507
Fax: +30 210 965 3934
g.kollias@fleming.gr

Andrew Nesbitt
UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE, UK
Tel.: +44 175 353 4655
Fax: +44 175 353 6632

Andy Popplewell
UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE, UK
Tel.: +44 175 353 4655
Fax: +44 175 353 6632

Mari Spitali
UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE, UK
Tel.: +44 175 353 4655
Fax: +44 175 353 6632

Sue Stephens
UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE, UK
Tel.: +44 175 353 4655
Fax: +44 175 353 6632