Clinical trials of antibacterial agents—a commentary

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Clinical trials are difficult to perform but are an essential prerequisite to establishing the efficacy and safety of a treatment intervention. They have an important role in protecting the public against ineffective or harmful therapies and are extensively used by the pharmaceutical industry in support of licensing applications of new drugs.

It is 8 years since the BSAC Working Party on Clinical Trials of Antibacterial Agents published its recommendations in this journal.\(^1\) This document provided an acknowledged stimulus for the Infectious Diseases Society of America (IDSA) to revise earlier outdated general guidance on trial design and to produce disease-specific guidelines for use in the development of anti-infective agents.\(^2\) This initiative was sponsored by the USA Food and Drug Administration (FDA). Contemporaneously, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) established a working party with a similar brief which agreed to harmonize its guidelines for use in the development of anti-infective agents.\(^3\) This working party added other disease-specific guidelines such as those concerned with trials of drugs for treating human immunodeficiency virus infection.\(^4\) In both the USA and Europe these guidelines have no official status, although they are used extensively by regulators, the pharmaceutical industry, trialists and even ethics committees. Thus, within the space of a few years there has been much debate and published guidance on the design and conduct of clinical trials of anti-infective drugs.

It is important to stress that these guidelines were never intended to be the final statement. In particular it is interesting to note that the statistical sections of the IDSA document generated considerable controversy during their development and hence it is not surprising that the report of the Statisticians in the Pharmaceutical Industry (PSI) Working Party, published in this edition of the Journal, has been produced.\(^5\) The report is a welcome addition to existing guidelines and extends, in a more pragmatic and complete manner, the statistical advice provided in earlier guidelines. However, in our view this document is unlikely to be the final word, in an area of therapeutics that is undergoing rapid change.

Clinical trials of anti-infective agents present a number of particular challenges, as a result of the intrinsic dynamics between the host, infecting organism and any therapeutic intervention. Studies of the treatment of site-related or disease-associated infections usually include a heterogeneous population. For example, a common therapeutic target, such as community-acquired pneumonia (CAP), includes illnesses caused by many different pathogens which vary seasonally, by underlying disease, and by virulence so that disease outcome is highly variable. Furthermore, although the management of CAP may take place within the community or in hospital, the criteria for admission to hospital are poorly standardized and are likely to differ between the centres where trials are conducted and, in turn, from the broader community where the antibiotic will be prescribed, once licensed.

Endpoints for clinical trials rightly focus on clinical efficacy and microbial eradication. These can be measured at various time points, e.g. after 7, 10 or 14 days’ therapy for many common infections, but up to 28–42 days post-therapy in the case of urinary tract infections. Outcomes such as the risk of relapse or superinfection and the rate of return to baseline health are rarely incorporated as meaningful endpoints in trial design.

It is also worth noting that placebo recipients show a high rate of spontaneous clinical cure for some infections. For example, in some patients pathogenic bacteria are eliminated from the middle ear by host defences alone, others with acute bacterial otitis media have persistent symptoms despite effective antibacterial therapy, while some improve despite the inability of a drug to eliminate the offending pathogen. Thus an antibiotic with modest antibacterial activity will appear to be almost as clinically effective as a more microbiologically active agent—the so-called ‘Pollyanna phenomenon’.\(^6\)

The advice captured in the PSI report is largely helpful and pragmatic for those undertaking clinical trials, particularly with regard to the way in which data might be...
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presented. The maintenance of a log of patients eligible for trial entry is stressed. However, we have some concern that the ‘per protocol’ analysis is emphasized as the primary analysis rather than the more conventional intention-to-treat analysis. Other analyses may be appropriate; these should be defined in the protocol in advance of the trial which should be sufficiently powered to accommodate additional analyses. Furthermore, any subset analysis should show consistency with the primary analysis. It is of interest to note that the report contains no discussion of the Bayesian approach to statistical analysis, despite its current popularity.

One concern is the emphasis the report places on the impact of ‘resistant’ pathogens on disease outcome. It is unfortunately all too common that breakpoints indicating susceptibility and resistance are set in advance of clinical evidence of efficacy. It should be remembered that breakpoints are a synthesis of information based on in vitro susceptibility and pharmacokinetic information, with appropriate adjustment where concentration-dependent safety concerns exist. Ideally, clinically relevant breakpoints should be decided once there is sufficient experience in treating defined infections with organisms requiring known inhibitory concentrations of drug, including those that might be considered of ‘marginal’ susceptibility. It would, therefore, appear inappropriate to exclude all patients with resistant pathogens from any evaluation, as suggested in the report. Regulators, microbiologists, prescribers and pharmaceutical companies all have interests in the results of treatment of less sensitive pathogens.

A further issue is the increasing recognition of the importance of pharmacodynamic studies in supporting proposed dosing regimens. These complement conventional pharmacokinetic information. Likewise it may be shown that site-specific data derived from studies of tissue penetration and intracellular disposition can also predict drug performance. Some of this information may not emerge until well beyond licensing. It is important, therefore, that statistical robustness should not negate any requirement for further evaluation of new agents once licensing has been achieved.

The Working Party supports the recruitment of patients who have failed other therapies, providing there is clear clinical and microbiological evidence of the infecting organism. This is welcome and endorses guidance provided in the IDSA and ESCMID documents. Another area in which the Working Party’s statements are to be applauded is the issue of confounding events. Within clinical medicine and, inevitably, within clinical trials confounding events arise which may prevent the full therapeutic potential of an intervention, be it favourable or otherwise, from being assessed in relation to outcome. This includes issues such as inappropriate antimicrobial therapy, inadequate medical or surgical management, underlying or unsuspected complicating disease, and the use of ‘do not resuscitate’ decisions at a time when the outcome remains unclear. These issues cannot be anticipated at the time of patient recruitment. The matter of confounding events has been emphasized recently in trials of therapeutic interventions in sepsis syndrome which have highlighted the importance of such events on trial analysis. This issue deserves wider discussion and a decision about the extent to which confounding events might be anticipated within a particular trial setting. Provided the sample size is adequate to accommodate them, the robustness of a particular trial might then be preserved.

The recommendation that patients with infections at more than one site be permitted entry into studies of one particular type of infection is pragmatic and particularly relevant to studies of intra-abdominal sepsis and of infections in intensive care unit patients. In contrast, the PSI Working Party appears to have avoided one other particular challenge, namely clinical trials in patients with neutropenic sepsis. This is unfortunate since it is one indication in which there are a large number of additional variables such as the nature of the underlying disease, the impact and recovery from cytotoxic therapy, infrequent microbiological confirmation of infection and the frequent use of systemically active agents for chemoprophylaxis. Efficacy in neutropenic sepsis is important for any new anti-infective drug since it often endorses the use of a new compound in other life-threatening infections.

One final area that deserves comment relates to the evaluation of drug safety. This is rarely the primary focus of any clinical trial and while information may be gathered both actively and passively on the spectrum of adverse events, trials are rarely designed to capture them in a statistically robust manner. The data gathered are often presented by body system and contrasted with data collected from patients receiving the comparator agent(s). However, information on the latter is not sufficiently standardized and may vary according to the target infection, its severity and host factors. Here again, no amount of statistical purity can compensate for poor quality information.

In conclusion, the science and practice of clinical trials of anti-infective drugs has made considerable progress in the past decade as a result of a number of thoughtful documents and guidelines. These have clearly influenced trial design and data submission in support of licensing applications of new drugs for the better. This process of evolution is still far from complete but, none the less, the PSI Working Party report is a welcome addition to this process.

References


