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Workshop on antibacterials

Report of the workshop

Workshop held on 7-8 February 2011 at the European Medicines Agency, London

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The aim of the workshop was to create a forum for discussion among stakeholders - academics, regulators, industry – around the European Medicines Agency (EMA) Draft 'Guideline on the Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections' (CPMP/EWP/558/95 rev 2, 2010), which is currently being finalised and was open for public consultation during 2010. The workshop looked at issues related to the clinical development of new antibacterial agents, including the design of studies in some of the major indications for use and studies targeting multidrug resistant bacteria.

The final agenda, list of attendees and presentations are available as separate documents.

The references used by the speakers are as stated on the slides.

The draft guideline is available on the Agency's website.

Chair: Jaap van Dissel
[Vice-Chair - Anti-infectives Scientific Advisory Group]

Co-chair: Marco Cavaleri
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This Report has been reviewed by the Infectious Diseases Working Party members.

DISCLAIMER

The views expressed in this Report are the personal views of the participating experts and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties. The official EMA position on the topic will be reflected in the revised version of the Guideline on the evaluation of medicinal products indicated for the treatment of bacterial infections.

Monday 7 February

Session 1. Non-inferiority studies and indication-specific primary endpoints

Regulatory consideration

Activities related to updating the current Note for Guidance on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 1, 2004) started with adoption of a Concept Paper by the Committee on Human Medicinal Products (CHMP) in February 2009. The proposal for a revision was prompted by accumulated regulatory experience indicating the need to clarify the CHMP's position on several important matters relating to antibacterial drug development. The current draft revision was released for consultation in February 2010. The consultation period was extended due to the plan to hold a workshop before finalisation of a version for adoption by CHMP.

The draft revision contains sections on microbiological data, the use of pharmacokinetic and pharmacodynamic (PK/PD) evaluations, clinical study design and the reflection of the clinical and microbiological data in the summary of product characteristics (SmPC).

The current draft revision of the guideline accepts that the clinical efficacy of antibacterial agents may be demonstrated in studies designed to assess non-inferiority (NI) of test agents vs. suitable comparator regimens for treatment of infections for which superiority studies are not feasible or not considered necessary. Acceptance of the validity of non-inferiority studies relies heavily on appropriate patient selection criteria and comparative regimens. The primary endpoint in such studies would usually be clinical and/or microbiological outcomes at a suitably timed test-of-cure (TOC) study visit.

It is preferred that at least two randomised and controlled studies are provided to support each clinical indication, although the provision of a single study may be acceptable if it meets the criteria stated in the CHMP guidance document on single pivotal studies. Non-inferiority margins are not specified but reference is made to the CHMP guidance on this issue.

Studies that have a primary objective of demonstrating non-inferiority may also be used to assess possible superiority provided that such an evaluation is performed in accordance with CHMP guidance.

Written comments received during consultation included requests to provide more detailed and indication-specific guidance on patient selection criteria, endpoints and non-inferiority margins and to consider how studies may be designed to satisfy the requirements of a range of regulatory agencies worldwide. The development of an addendum to the 'core' guidance document (i.e. CPMP/EWP/558/95 rev 2) to address these matters is currently under consideration by the CHMP-appointed Infectious Disease Working party (IDWP).

Hospital-acquired and ventilator-associated pneumonia (HAP/VAP)

Academia: J. Chastre

In HAP/VAP clinical studies the primary endpoint has usually been cure at a TOC visit based on the subjective assessments of the investigators. Clinical cure is not the best primary endpoint to use in HAP/VAP studies according to the opinions expressed in the August 2010 supplement in *Clinical Infectious Diseases*[1] that considered the design of HAP/VAP studies and the FDA Guidance for

[1] Recommended design features of future clinical trials of antibacterial agents for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Spellberg B, Talbot G. Clin Infect Dis. 2010 Aug 1;51 Suppl 1:S150-70.

Industry[2] issued in 2010. Instead, the selection of all-cause mortality (ACM) on study day 28 has been recommended as the primary efficacy endpoint.

Several studies have demonstrated that mortality rates increase with inappropriate initial therapy for VAP. No placebo controlled studies have assessed the beneficial effect on ACM of antibacterial therapy for HAP/VAP. In 12 non-randomised studies the reported ACM rates when initial treatment was inappropriate for the pathogens recovered were approximately 50-60% and these data can be used to estimate the effect of no treatment. In nine randomised active-controlled studies the ACM rates were approximately 20-30% in patients considered to have been treated adequately.

Thus, cross-study comparisons suggest that the difference in ACM at day 28 for active treatment vs. placebo is around 30%. This suggests a non-inferiority margin of 10% is appropriate for this endpoint provided that the day-28 ACM is around 20% and that the margin is applied to the subset of patients with a documented pathogen.

Using this approach for the primary analysis, the secondary endpoints could include clinical response at TOC, ACM at day 14, the number of days with no ventilation and with no antibacterial therapy and changes in clinical pulmonary infection score (CPIS) and procalcitonin level from baseline to TOC.

There is a need to better define clinical success and failure. Failure could be based on the rise in CPIS by at least 2 points on day 3, the CPIS not dropping by at least 2 points on day 10, the need for active antibacterial treatment after day 10 and death or the re-starting of antibacterial therapy before day 10. Clinical success could require improvement or no worsening of radiographic findings and resolution towards normal of CPIS components, including volume and purulence, fever, white blood cell counts (WBC) and partial pressure of oxygen (PaO2) in addition to an assessment of clinical status.

Industry: R. Fromtling

The clinical study endpoints should be relevant to both patients and their physicians and should be selected to assess the effectiveness of antibacterial agents in feasible clinical studies. The selection of primary endpoints and non-inferiority margins should allow for achievable sample sizes when enrolling patients who developed HAP/VAP in hospitals, nursing homes and intensive care units (ICUs). Pre-study exposure to antibacterial therapy should be limited but should not be an absolute exclusion criterion. Realistic and informative studies in HAP/VAP should enrol only patients for whom there is strong evidence for that diagnosis.

The response to treatment should be assessed before underlying conditions influence the outcome which is why early assessments (e.g. on days 7-14) are better than later time points (e.g. day 28). While ACM on day 28 could be one of the pre-defined study endpoints this has some limitations as a primary endpoint.

Attributable mortality would be a preferable endpoint to ACM due to the influence on ACM of supportive care measures and underlying patient conditions.

ACM is not an outcome routinely considered in clinical practice and does not reflect commonly used modes of assessing the progress of patients with HAP/VAP, such as measurement of fever and oxygenation status. For example, the PaO2/FiO2 ratio has been shown to be linked to a fatal outcome in this patient population and is closely monitored in ICUs.

The 2010 recommendations for use of ACM at day 28 as the primary efficacy endpoint and a 10% non-inferiority margin was accompanied by several caveats regarding the population in which the primary analysis should be performed. If ACM at day 28 is chosen as the primary efficacy endpoint the historical data (which suggest an approximate 30% effect of treatment) could also support a 15% non-

[2] Guidance for Industry:Hospital-Acquired BacterialPneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf

inferiority margin, which would reduce the sample size required. The application of the ACM at day 28 endpoint and a 10% non-inferiority margin to the sub-population with a documented pathogen can be questioned since a modified intent-to-treat (mITT) population, defined by all treated patients meeting the minimum criteria for diagnosis of HAP/VAP, is more representative of clinical practice (as only about 30-40% of patients considered to have HAP/VAP actually have a pathogen). This MITT definition avoids the uncertainties surrounding the microbiological findings. For example, failure to recover some or all organisms from samples and inherent errors in estimates of colony-forming units per ml.

The primary analysis should be in all treated patients meeting the diagnostic criteria for HAP/VAP. Efficacy in all treated HAP/VAP patients with a pathogen should be evaluated in a subset analysis perhaps with a pre-defined minimum number or percentage of total patients with a pathogen to be enrolled. There should be acceptance of culture and non-culture based methodologies to detect pathogens in blood and in a range of respiratory specimens. HAP and VAP do not need to be studied separately provided that there is pre-defined stratification. A very strict exclusion of patients who received antibacterial therapy before enrolment will make the conduct of such studies less feasible and limit generalisation of the results to actual clinical situations. If patients who received other (potentially active) antibacterial agents within a specified time (48 h) of randomisation are included, there could be stratification on this basis at enrolment to achieve balance between treatment groups.

Academia: P. Ambrose – Considerations for an appropriate non-inferiority margin in HAP/VAP studies

The rational design of non-inferiority studies with antibacterial agents requires some knowledge of the magnitude of effect of active treatment and the application of clinical trial endpoints that capture the benefit of treatment . There are many limitations to using historical data to estimate the no-treatment effect (e.g. lack of a placebo group, lack of prospectively randomised and double-blind studies, use of various medical interventions of unknown value and lack of source documentation to assess the validity of the findings).

The statistical approach to using historical data to assess the no-treatment effect has been based on frequentist inference. Until recently there has not been a detailed consideration of the use of either frequentist inference (in which the mean is considered to be a real value and results are determined only by the study data) or Bayesian inference (in which the mean is not considered as a fixed value and prior information on the likelihood of the mean to fall within specified intervals can be taken into account) combined with pharmacometric methods.

The utility of frequentist and Bayesian pharmacometric-based logistic regression analyses in determining the magnitude of treatment effect and in assessing the ability of clinical endpoints to capture benefit has been assessed using data from a relatively recently completed Phase 3 HAP/VAP study with tigecycline. The application of a Bayesian approach to tigecycline data was justified based on the observation that the free drug AUC_{0-24}/MIC ratio has been shown to correlate with outcome in animal infection models and in treated patients.

Using the statistical approaches described, and applying them to 61 patients with sufficient PK data for inclusion in the analyses and with highly concordant clinical and microbiological outcomes, the difference in likelihood of success at high and low plasma exposures was estimated. The function associated with the frequentist analysis was steeper and resulted in a larger estimate of the treatment effect (60%) than that of the Bayesian (40%). However, the 95% confidence bounds around the functions were much tighter using the Bayesian approach and resulted in a larger M1 estimate. The M1 estimate was calculated using a boot-strapping approach rather than the subtraction of interval estimates as is done in standard M1 calculations.

The results using either frequentist or Bayesian approaches indicated that clinical outcomes (success/failure endpoints) captured a measure of treatment effect such that there is no need to resort to historical data. The best estimate of treatment effect was from about 40-60% for HAP/VAP. Since the patients who failed did have some treatment exposure the estimates of no-treatment response could be viewed as conservative.

The use of pharmacometric methods is proposed as a means of using contemporary clinical study data to justify non-inferiority margins without need to resort to historical data and all its uncertainties.

Discussion

There was some support as well as some concern expressed for the view that ACM at day 28 in patients with a pathogen should constitute the primary analysis in HAP/VAP studies.

Designating ACM at day 28 as the primary efficacy endpoint could increase the risk of not detecting a difference between treatments even if there is one, because the main driver of ACM may be underlying conditions rather than failure of treatment for HAP/VAP. Hence mortality at day 14 might be a more sensitive endpoint, while disease-free survival could also be considered.

Patients who have their antibacterial therapy changed because of lack of response but survived would be counted as a success in an analysis of day 28 ACM while they would be counted as failures in the analysis of clinical outcome at TOC. Focussing the study findings on ACM might diminish the importance of clinical outcomes. This conflicts with the traditional appreciation that success equates with a favourable clinical outcome for the infection that was treated. Clinical response closely correlated with drug exposure in the pharmacometric analysis that was presented.

Attributable mortality is of much more interest to physicians than ACM. There may be scope for better use and/or exploration of the usefulness of modern technology in assisting in the assessment of HAP/VAP outcomes (e.g. lung scanning techniques). Speed of recovery (time to reach endpoints associated with cure/improvement) is also of considerable clinical relevance.

There was some support for restricting the primary analysis to patients with a pathogen. However, this means that the analysis would be conducted in a relatively small subset of the all-treated population, which does not equate with the actual patient population receiving antibacterial agents for HAP/VAP in clinical practice. It may be queried whether it is rational to distinguish analyses of outcomes for those patient subsets with/without a pathogen (i.e. what is the evidence that these patients are really different).

In addition, microbiological evaluations do not always reveal the causative pathogen(s). For example, negative cultures of appropriate specimens do not necessarily rule out the possibility that the patient has a bacterial infection. It may be difficult to identify the major pathogen(s) when several bacterial species are isolated from a specimen and/or from a range of different specimens (distinguished by site, type of specimen and/or time) obtained from an individual patient. There are no widely-accepted criteria for classifying organisms as ‘‘true’’ pathogens in these cases.

Enrolling only patients who have had no prior therapy is not feasible. The possible effect of some prior therapies on outcomes could be addressed by stratification of randomisation.

Scientifically-sound methodologies to evaluate non-inferiority margins that avoid some of the uncertainties and questions regarding the relevance of historical data to current practice, were welcomed (e.g. such as those suggested by the pharmacometric approach that was presented). The analytical approaches presented have been applied to datasets derived from studies in other types of infections and have been shown to be useful. There is a need to further explore these approaches.

Complicated skin and soft tissue infections (cSSTI)

Academia: M. Dryden

Clinical and microbiological endpoints should continue to be the focus of assessments of treatments in cSSTI studies. In particular the selection of clinical outcome at TOC as the primary efficacy endpoint remains valid. This approach allows for detection of failures of therapy and an assessment of relapse rates. Microbiological outcome at TOC is an important secondary endpoint, and adequate sampling of infection sites is required. Clinical and microbiological outcomes should also be documented at end of therapy (EOT) and assessed in secondary analyses.

A primary comparison between treatments based on the clinical findings after 2-3 days of treatment may not be useful and may be a cause for concern.

Industry: J. Rex

Early endpoints (e.g. at 72 h after starting assigned treatment) are effectively incorporated into later endpoints (assessed at TOC visits). Physicians always take note of patients' early response to treatment and such data are collected and reported during clinical studies. Nevertheless, the patient outcome at TOC is what matters to the patient and the physician.

The types of infections that are treated in studies should be representative of the range of cSSTIs encountered in routine clinical practice.

Requiring fever for enrolment may lead to the elimination of a large proportion of patients presenting with cSSTI from studies. For example, some studies have reported very low rates of fever (10-15%) in potentially suitable patients. Sponsors should document the severity of infection at baseline and the potential for progression in individual patients taking into account not only fever but also evidence such as systemic inflammatory response syndrome (SIRS) scores and co-morbidities recognised to influence outcomes.

Patients with major abscesses should be eligible but it is reasonable to restrict the proportion of patients with abscesses that are enrolled in any one study. Setting strict requirements for the minimum area of cellulitis may lead to an unrepresentative patient population because lesions in some body parts may not meet the criteria. In addition, size is only one of several possible indicators of severity that should be documented.

In all types of cSSTI except abscess the treatment effect is large and a NI margin of 10-15% applied to clinical cure at TOC can be justified. A margin of less than 10% would lead to non-feasible study sizes.

Erysipelas-related mortality over the period from 1880-1960 provides information on the effect of availability of antibacterial agents. Effect size estimates range from 42% for wounds and ulcers to 29% for cellulitis and erysipelas combined.

Discussion

Clinicians want to know that the new agent is effective in the severely ill population with cSSTI. There are recognised difficulties in assessing the severity of cSSTI in clinical trials. Particular features of the study populations (such as low percentages with positive blood cultures, exclusion of some types of infections) are mentioned in section 4.4 of SmPCs but it is unclear to physicians how this affects the suitability of the agent for treating the full range of cSSTI encountered. While patient selection criteria might be used to enrich the study population, for example by requiring certain signs and symptoms to be present at baseline or by setting minimum limits for patients with specific diagnoses, these approaches would not produce a truly representative population.

Requiring that eligible patients be febrile would exclude many of those with cSSTI and could potentially impact recruitment among the elderly, who are less likely to develop fever in response to infections and may be hypothermic if they are severely ill. Afebrile patients should meet other criteria to justify eligibility for treatment.

Patients with abscesses should be eligible for cSSTI studies because they are part of the spectrum but it would be reasonable to limit numbers using stratified enrolment. Inclusion criteria should specify that investigators must consider that these patients still need treatment after drainage.

Relatively few patients enrolled in cSSTI have a diagnosis of erysipelas. It is rare to isolate an organism because there is nothing obvious to swab/sample for microbiology and few patients have a positive blood culture. There was some support for lesion biopsies in these cases but also concern that the results are not reliable.

Relapse rates are usually very low in cSSTI studies and most failures occur relatively early on during treatment but not necessarily within the first two to three days. A primary analysis of outcomes at TOC has the advantage of capturing both failures and relapses. Since almost all bacteriological outcomes in cSSTI are presumed based on clinical outcomes, information gathered on the few patients who have documented persistence can be very informative. Data from these patients should be explored in detail.

A clinically acceptable non-inferiority margin should not be more than 15% but there is no need for a margin less than 10%. Pharmacometric analyses along the lines presented for HAP/VAP have estimated the treatment effect to be about 40%. The estimate of treatment effect (and hence an appropriate non-inferiority margin) is determined by the heterogeneity of patient response but if less heterogeneous populations are enrolled into studies there are inevitable problems for extrapolation of the results to all cSSTI patients. Evaluation of factors that are most strongly associated with outcome may assist in identifying patient selection criteria for future studies, but these factors may not as yet have been explored sufficiently.

Traditional clinical cure endpoints at TOC are still valuable as primary endpoints, while further exploratory endpoints (such as those based on biomarkers or outcomes evaluated at different time points) could be investigated as possible alternatives if they can be adequately validated. In any case, the use of the same studies to satisfy different recommendations for primary endpoints by regulatory authorities can be addressed by selecting the primary endpoint for the study protocol that would require the largest sample size and then developing separate statistical analysis plans for application to the data. However, this approach will not solve differences in requirements for patient selection criteria and further consideration of this issue is needed.

Session 2. Superiority studies: placebo- and active-controlled

Major indications: acute otitis media (AOM), acute bacterial exacerbation of chronic bronchitis (ABECB) and acute bacterial sinusitis (ABS)

Regulatory consideration

The current draft revision of the guideline refers to the unreliability of non-inferiority studies in assessing the efficacy of an antibacterial treatment that has not been shown to be consistently superior to placebo in a defined patient population (which may be a small subset) with a specific infection type. Currently this situation would apply to acute bacterial (maxillary) sinusitis (ABS), acute bacterial exacerbations of chronic bronchitis (ABECB) and for some types of infections often treated with topical agents (e.g. superficial skin infections). The current draft also includes acute otitis media (AOM).

However, since the draft was released for consultation additional data of relevance from placebo-controlled studies in well-defined patient populations have become available.

In these infections the demonstration of superior efficacy of a test agent versus placebo would provide the most robust evidence of clinical benefit. While the difficulties of conducting placebo-controlled studies in some types of infections are recognised there is a paucity of data available to define sub-populations in which a non-inferiority study design and appropriate margin could be justified. The incorporation of a third active treatment arm in placebo-controlled studies is suggested although not with the intent of demonstrating non-inferiority of test vs. active.

Alternatively, superiority of the test agent should be shown against an active comparator for at least one endpoint that is considered to represent an important clinical benefit (e.g. time to resolution of specific signs and symptoms).

Written comments have included: requests to provide specific examples of endpoints in superiority studies against active comparators; opinions that it is unlikely that superiority could be shown against active comparators based on any endpoint; and proposals that sub-populations may be identified within some indications in which non-inferiority studies should be accepted as sufficient evidence of efficacy.

Discussion on specific indications:

Acute bacterial exacerbation of chronic bronchitis:

Industry: F. Boer

The population in which placebo-controlled studies are possible consists of low-risk-patients in which superiority vs. placebo is least likely to be demonstrable since these patients commonly respond to non-pharmaceutical measures. Issues surrounding equipoise are important to assess the feasibility of placebo-controlled studies in patients with certain clinical features that some physicians would consider point to a likely benefit from antibacterial therapy. Guidelines from professional bodies are not aligned in their recommendations for adding antibacterial therapy to other measures.

Active-controlled studies are not likely to show superiority for a test agent regardless of the efficacy endpoints. There is no validated Patient Reported Outcome (PRO) instrument at present for ABECB.

Attempts to develop antibacterial agents for prophylaxis of ABECB are also limited because there is no consistent opinion on their usefulness in this setting and no widely accepted definition that could be applied to breakthrough cases. In addition, uniform risk stratification strategies are lacking.

Resistance to antibacterial agents continues to increase and there is a need for new therapies. With no clear regulatory guidance for ABECB studies it seems unlikely that new agents will be evaluated for use in this indication. There is a considerable need for better definitions of ABECB and for better means of defining patient populations who should be treated in clinical studies.

Discussion

At present it is not possible to define the sub-population of ABECB patients that would actually benefit from therapy. Investigators would not risk treating patients with placebo if they had features considered to warrant the institution of antibacterial therapy, and such studies are unlikely to be feasible or ethical. The same situation would apply to studies in which the control arm received a delayed start regimen. There is a need for academia-driven studies to properly assess the value of active treatment.

There is a need for oral agents that are active against organisms resistant to commonly used agents, but it is not possible to perform a superiority study in which patients might knowingly be assigned to a comparative agent to which pathogens are resistant or very likely to be resistant. A new agent that is active *in vitro* against organisms resistant to commonly used antibacterial agents might be assessed in patients who have already failed other antibacterial therapies but the feasibility of collecting enough patients is doubtful. A comparative design would require the availability of another potentially active and suitable agent, and an uncontrolled design would probably not be sufficiently informative in this case.

Other possibilities might include consideration of study designs that have been used in other areas such as those used to assess the role of anti-inflammatory agents in patients with chronic obstructive pulmonary disease (COPD). These may provide some ideas for studies in AECB. Studies that examine a wide range of dose levels of the test agent and demonstrate a strong relationship between exposure and response might provide some insight into treatment effect.

Obtaining an indication for treatment of ABECB represents a path for use of an oral antibacterial therapy in adults. There have been several examples in which antibacterial agents have initially reached the market for indications such as ABECB but in later years have been shown to have an important role in the treatment of a range of infections. If they had not reached the market by this route some useful therapeutic interventions might never have come to light. A clear and feasible regulatory pathway for bringing such agents to market should be developed.

Acute otitis media / acute bacterial sinusitis

Academia: R. Cohen

There is no consensus on the role of antibacterial agents in the management of AOM within the EU. A range of placebo-controlled studies has been performed but there has been no consistent demonstration of benefit for active treatments. To some extent this may reflect features of the study designs and conduct such as a lack of precise diagnostic criteria, investigators who were inexperienced in otoscopy, small sample sizes, very mixed populations (e.g. age ranges) and unclear definitions of outcomes.

Two placebo-controlled double-blind studies[3] in well-defined populations of young children with AOM have been published recently. The studies paid careful attention to the diagnosis of AOM and outcome assessments but they did not include tympanocentesis. The results showed a benefit for active treatment. The findings mean that placebo-controlled studies are now difficult and very likely impossible to perform in comparable patient populations (i.e. in terms of age range and diagnostic criteria) with AOM. The identification of a benefit for active antibacterial treatment in these studies eliminates the need for a placebo control group if the patient selection and assessment criteria are carefully addressed in the protocol.

There is a high spontaneous resolution rate in ABS. Across 13 placebo-controlled studies in ABS the clinical cure rates with no active antibacterial treatment were 8% on days 3-5 but increased to 35% on days 7-12 and 45% at 2 weeks. Active treatment improved the observed cure rates at 7-12 days with an absolute rate difference of 15% (95% CI 4%, 25%). A review of ABS studies indicated clinical improvement on placebo for 30% at days 3-5 and 73% on days 7-12 with active treatment effects of 14% at 7-12 days and 7% at 2 weeks.

[3] Treatment of Acute Otitis Media in Children under 2 Years of Age, Hoberman A et al, N Engl J Med. 2011 Jan 13;364(2):105-15.

A placebo-controlled trial of antimicrobial treatment for acute otitis media, Tähtinen PA et al, N Engl J Med. 2011 Jan 13;364(2):116-26.

In AOM and ABS, bacterial eradication studies are not easy to perform but are especially interesting to assess the effects of new agents on pathogens resistant to commonly used antibacterial therapies.

Industry: S. Rohou

Based on the two recently published placebo-controlled AOM studies, uncertainty regarding the role of active therapy has now gone, so equipoise has been lost and placebo-controlled studies cannot be performed. The authors of one of these studies had previously pointed out that consent was refused for about two-fifths of otherwise eligible children. The endpoints used in these studies were composite and should be analysed in more detail than is available from the publications but the sub-components of the composite endpoint do seem to point to a consistent effect of active therapy. In future active comparative studies in AOM the non-inferiority margin should not be more than 10%.

The alternative, performing a superiority study against an active comparator, is unlikely to succeed even when using a primary endpoint such as time-to-resolution of specified events. For example, superiority against a properly dosed beta-lactam agent is not expected to be demonstrable for any endpoint of clinical relevance. A design that employs delayed rescue therapy is ruled out due to lack of equipoise.

New agents will not be developed for AOM unless non-inferiority studies are accepted along with non-inferiority margins that lead to feasible studies. In the past, AOM has been the gateway indication for oral antibacterial use in children and a clear regulatory path is needed.

Parallel issues apply to studies in ABS, in which there is a risk of suppurative complications and equipoise is probably limited. Because of the lack of high quality information on the magnitude of the treatment benefit and of a clear regulatory path, the development of new antibacterial agents for use in this indication seems unlikely at present.

Discussion

Placebo-controlled studies in AOM are no longer possible in children below 2-3 years of age but a wait-and-see approach is likely still possible for older children. Even in countries with high thresholds for starting antibacterial therapy the rates of mastoiditis complicating untreated AOM are very low.

The patient selection criteria are critical in AOM studies. The published studies that have shown a benefit have been conducted in a carefully defined sub-population of all children that could be considered to have AOM.

The AOM populations enrolled in the published studies were defined by signs and symptoms that, in the absence of bacteriological data, were intended to identify those who really had the disease. Extrapolation from such a population to one with less signs and symptoms should be possible, particularly within the same age range.

There are 28 antibacterial agents already approved for AOM in the EU where many countries still have very low pneumococcal resistance rates. There is scope for comparing routine with high doses of approved antibacterial agents in AOM as well as assessing new therapies.

Obtaining microbiological data is desirable since only children with bacterial pathogens really need antibacterial therapy but demanding tympanocentesis (even a single tap at baseline) is perceived to be difficult. Double-tap studies have shown the benefit of co-amoxiclav vs. cefaclor. It seems likely that few investigators would agree to participate in second-tap studies (especially in the EU) although these might still be possible in countries with high burdens of AOM complications (e.g. in Latin America).

In ABS a major limitation is the lack of documentation of treatment effect in a well-characterised patient population that might benefit from antibacterial therapy. Studying small numbers of cases intensively may be a better alternative to the types of studies that have been performed in larger

numbers and might serve as core evidence of efficacy. Small scale studies have been performed in which sinus tap was followed by sinus catheterisation that allowed serial sampling to determine drug concentrations and cytokine levels as well as bacterial load. The data collected were then evaluated against overall clinical and microbiological outcomes. Time-to-sterilisation would perhaps be an appropriate endpoint for such studies.

There is a continued need for new oral agents even though not all countries are experiencing resistance rates affecting the usefulness of available antibacterial therapies. There is a need to look to the future and to take into consideration the fact that initial marketing of oral antibacterial agents for indications such as ABECB, AOM and ABS has often led to later exploration of such agents in the management of a range of infections.

Session 3. Evaluating new agents for rare or multidrug resistant pathogens

Possible study designs and possible scenarios depending on total spectrum and indications granted/sought

Regulatory consideration

Since 2004 EU regulatory guidance has acknowledged the possibility of licensure for a new antibacterial agent based on limited data if it appears likely to be clinically active against problematic resistant organisms, difficult to treat and/or rare pathogens. The current draft revision gives consideration to circumstances in which no clinical data can be provided (e.g. inhalational anthrax).

There is a separate consideration of instances in which only very limited numbers of cases of infection with specific pathogens are likely to be treated even in studies that actively seek to enrol patients with these types of infection. It is expected that at least limited clinical data should be provided to support claims for efficacy against such organisms. Depending on how frequently such pathogens are encountered, a range of possible approaches to obtaining such data can be envisaged. While provision of only uncontrolled data is viewed as a last resort, consideration is given to the possibility of collecting data in randomised studies with lower than standard levels of statistical power or of collecting evidence of efficacy in one or more indications using standard non-inferiority design approaches supplemented with data on specific target pathogens from smaller studies, which may have to be uncontrolled.

Comments received have included: proposals for the possibility of pooling data across a range of different infections due to specific pathogens; requests to specify the numbers of treated cases that would be required to support specific claims; and requests for the possible granting of pathogen-specific rather than indication-specific (i.e. type of infection specific) indications.

Academia: A. Pefanis (for H. Giamarellou)

Multi-drug resistant (MDR) pathogens may be defined as being resistant to at least three major classes of antibacterial agents. Within the EU some countries now encounter pan-drug resistant (PDR; against which no available licensed therapy is active) organisms and extensively drug-resistant (EDR) organisms (i.e. treatable with only one or two possible classes/agents). The treatment of MDR/EDR pathogens is an area in which rapid diagnostic techniques are particularly valuable in directing early treatment until the infection is culture-proven and traditional susceptibility data are provided.

Patients with such organisms are most often already in ICUs and have confounding factors that limit the assessment of the effect of antibacterial therapy. Enrolling patients with MDR/EDR pathogens into routine indication-specific randomised studies is not possible due to the unsuitability of commonly used

comparator regimens and the lack of data to identify optimal regimens for potentially suitable comparators such as colistin and fosfomycin. For example, there is some evidence that recommended regimens of colistin are insufficient).

Enrolling patients with MDR/EDR pathogens into a study targeted at gathering data on the efficacy of a new agent against organisms with particular resistance profiles would not be feasible if this is limited to any one type of infection due to the numbers encountered. Including them in a study in which the initial comparative treatment is selected to cover MDR/EDR pathogens would mean that many patients enrolled would receive these unusual therapies when they do not require them (with implications for antibacterial stewardship) and protocols would have to allow for switching regimens in the comparator group once susceptibility test data were available.

At present no clear and feasible clinical study design can be recommended for assessing the clinical efficacy of a new agent targeted at MDR/EDR pathogens. Data gathered from co-operative registries might assist in determining possible approaches to studies in such patients and appropriate treatment regimens.

Industry: M. Goldberger

There is a need to facilitate the development of new agents for the treatment of resistant and/or rare pathogens. Focussing on the quality and not quantity of the clinical development programme is a way forward, acknowledging that this will inevitably mean a trade off due to inevitable uncertainty surrounding the overall performance of a new agent at the time of first approval.

For an agent that seems likely to be suitable for treating serious infections due to MDR organisms there should be a strong focus on the microbiological data and PK/PD analyses to help compensate for a limited clinical programme. Clinical efficacy data are valuable for infections due to wild types as well as those due to pathogens with MDR phenotypes. In this way, evidence of efficacy in patients whose clinical condition is comparable with that expected in the population most likely to have MDR pathogens can be added to the microbiological and PK/PD evidence to provide a strong likelihood for clinical efficacy.

It is important to conduct at least one randomised controlled study that is not targeted against MDR pathogens only in at least one major indication relevant to the spectrum of activity and PK properties of the new agent. Such studies provide an opportunity to obtain controlled safety and efficacy data and can be used to evaluate the performance of the agent in a severely ill patient population. Ideally the indication(s) studied would be likely to include at least some patients infected with the types of MDR pathogens of most interest. If a new agent is active against only one or very few species a controlled study may still be possible but would require implementation of rapid diagnostic techniques pre-randomisation.

Depending on their frequency, very few patients infected with the target MDR pathogens may actually be enrolled in the controlled clinical study or studies. Additional data on efficacy of a new agent against target MDR pathogens may be needed to support its use but major difficulties are expected when attempting to obtain such data from randomised comparative studies, especially if these are indication-specific. The type of study or studies in which additional data specific to MDR pathogens could be collected will have to be considered on a case-by-case basis in accordance with the properties of the new agent.

Discussion

In some EU centres investigators can no longer enter patients into randomised controlled studies in some indications that employ commonly used comparator regimens because the rates of MDR/EDR

pathogens are too high. This may severely limit the numbers of target MDR/EDR pathogens that can be treated with a new agent during clinical development programmes.

The possibility of performing indication-specific randomised controlled studies to assess overall safety and efficacy and supplementing these data with evidence for efficacy against MDR/EDR pathogens from single-arm studies raises questions regarding the acceptability of uncontrolled data and the pooling of data for specific MDR pathogens across infection sites. There was both support and concern expressed regarding proposals to allow pooling of efficacy data for individual MDR/EDR pathogens across indications. Pooling across body sites where PK might be expected to be comparable was perceived as reasonable. Pooling across all body sites was perceived as more problematic.

A possible study design for studying efficacy against MDR pathogens might be to compare an optimised regimen (OR) derived from licensed agents with the test agent alone or added to OR, depending on the spectrum of activity of the test agent and the species that might be treated. Such an approach might be particularly pertinent for new agents with very narrow antibacterial spectra of activity since these will likely be used in combination regimens. In addition, if a new agent targeted *P. aeruginosa* then monotherapy with a test agent would not be acceptable for the majority of infection types since this would not be in line with usual clinical practice. In such instances the OR could be viewed as standard of care and treated as a single comparator in the analysis. Depending on the circumstances it might be possible for protocols to reasonably limit the options for agents to be included in the ORs.

The relatively small safety database that might result from the approach suggested might be acceptable for supporting an initial conditional approval. This would be considered on a case-by-case basis taking into account the perceived benefit and the unmet clinical need.

There are additional issues for the clinical development of new agents that do not have a direct antibacterial action or have two modes of action, including activity against a bacterial target. These therapies are expected to be administered in conjunction with other antibacterial agents and this will add to the complexities of a rational clinical development programme and the assessment of the contribution of the test agent to outcomes.

Tuesday 8 February

Session 4. Consideration of some other specific indications

Regulatory consideration

Prompted by requests for scientific advice and regulatory decisions the draft revision considers examples of indications that pose some special problems in terms of data requirements and how to reflect what has actually been demonstrated in clinical studies in SmPCs. The examples include claims for treating bacteraemic patients, neutropenic patients suspected of having a bacterial infection, catheter-related infections and eradication of carriage.

With regard to bacteraemia, the working definition refers to the isolation from blood cultures of one or more species likely to be responsible for or contributing to the clinical signs and symptoms of infection. The granting of an indication for use in bacteraemia, either unqualified or pathogen-qualified, is considered highly problematic since this would imply that the antibacterial agent could be used in any patients with bacteraemia or in any patients with bacteraemia due to a specific pathogen regardless of the known or unknown primary foci of infection. In the context of three recent procedures[4] for the harmonisation of the SmPC for approved intravenous antibacterial agents ('article 30 referral', as per article 30 of Directive 2001/83/EC of the European Parliament and of the Council) the CHMP considered that the totality of evidence for use could support an indication for the treatment of bacteraemia that occurs in association with, or is suspected to be associated with, infections falling within the clinical indications for use. Comments received have generally supported this approach but have also questioned the level of evidence that would be required to obtain such a claim for new antibacterial agents.

The guidance currently states that indications referring to eradication or reduction in numbers of pathogens from specified body sites cannot be accepted unless the microbiological effects can be related to a measurable clinical outcome. Placebo-controlled studies that demonstrate a clinical benefit linked to the microbiological effect are therefore required unless the type of intervention under study is already widely established as standard-of-care and the microbiological surrogate endpoint has been validated. The need for fully-validated microbiological techniques and definitions of terms is stressed as well as the need for measuring the duration of any effect (e.g. post-treatment period during which no positive cultures are obtained). Comments have included proposals that eradication of carriage should be viewed *per se* as a clinical benefit and that reduction in inter-patient transmission should be taken into account.

Bacteraemia

Academia: H. Seifert

Bacteraemia is a microbiological definition/finding and is not an infection *per se*. Bloodstream infections may be defined as bacteraemia that occurs in association with clinical manifestations of infection. In a study in Cologne in 1997-98 at least one third of cases had no identified primary focus while about 40% were thought to be catheter-related bloodstream infections (CRBSI) and the rest were associated with a variety of foci. Looking specifically at *S. aureus* bacteraemia, a study of 417 cases in 2006-2008 reported that 25% had no focus, about one third were catheter-related and the rest had a variety of foci.

[4] Piperacillin-tazobactam, Ceftazidime and Imipenem-cilastatin

Bacteraemia is uncommonly detected during controlled clinical studies in major indications such as community acquired pneumonia and cSSTI. Dose regimens suitable for non-bacteraemic patients may not necessarily be suitable for those who do have bacteraemia. There is a need for specific studies in patients with bloodstream infections.

Industry: J. Rex (for M. Kunkel)

The definition of bacteraemia in the revised draft guidance document and the need to link bacteraemia to the indications for use is generally agreed. *S. aureus* bacteraemia (whether the primary focus is known or unknown) should be considered separately since it constitutes a unique medical entity.

Bacteraemia with *S. aureus* comprises a spectrum of conditions such that no sub-group is large enough for a dedicated study. A single study that enrols patients regardless of whether the primary focus is known or unknown (but excluding CRBSI) should be sufficient to support an unqualified indication for the treatment of bacteraemia due to this species, based on pooling data across all types of patients enrolled.

In such an 'all-comers' study there may be dose regimen issues for individual indications. In addition, there will be a need to adjust the duration of treatment depending on the foci of infection (e.g. endocarditis and osteomyelitis require special considerations).

CRBSI could be studied as a subset of cSSTI patients with any catheter-related infection (CRI). Past experience suggests that such a study would likely take a long time to complete recruitment.

Discussion

A small percentage of patients with infections that fall within the major indications for use of parenteral antibacterial agents actually have documented bacteraemia. The clinical cure rates observed for an agent when used to treat patients with foci of underlying infection associated with bacteraemia cannot necessarily be extrapolated to any patients who happen to have a bacteraemia with the same pathogen.

While the exclusion criteria employed in randomised clinical studies in major indications could possibly reduce the chance of enrolling bacteraemic patients, no clear evidence supports this. For example, the proportion of cSSTI associated with bacteraemia does indeed appear to be low regardless of patient population characteristics.

S. aureus bacteraemia merits separate consideration and there is a need for a specific regulatory view. An all-comers study based on documented *S. aureus* bacteraemia in a comparative design and using one dose regimen but with durations tailored to infection type was proposed to support wording for use in *S. aureus* bacteraemia that is not tied to the other indications. However, it was pointed out that the CHMP has not granted bacteraemia qualified only by species as an indication for use in the past, despite submission of data as suggested above. Further consideration of a possible acceptable level of evidence to support such an indication would be needed.

The assessment of appropriate durations of treatment is important for all indications and exploration of duration is encouraged by EU regulators. While the range of durations that are evaluated in clinical studies may be limited, recent advancements in the use of hollow-fibre models may assist in the selection of an appropriate range of treatment duration for clinical efficacy studies.

Elimination of carriage

Academia: A. Andremont

The eradication of carriage of specific types of bacteria should be viewed *per se* as an indication because carriage is a prerequisite for clinical infection and eradication of carriage prevents infections and interrupts transmission.

To require demonstration of a clinical benefit as a result of eradication of carriage would need large trials because the clinical events that might be prevented are very rare. Thus an alternative and feasible endpoint would be reduction of colonisation, which would facilitate the conduct of small and low cost trials. An alternative clinical study endpoint could be reduction of dissemination, which would also lead to manageable sample sizes and has public health relevance.

Industry: K. Barker

Some EU countries have marketed products with indications for eradication of *S. aureus* in the nose, *N. meningitidis* from the nasopharynx and *H. pylori* from the gut. Eradication may refer to a short term effect on numbers of organisms during high-risk periods for infection and to a reduction in bacterial load. However a negative culture does not necessarily mean that there has been complete elimination of the target bacteria. The risk of re-appearance of an organism and time to recolonisation can be expected to vary by organism and body site.

If a study was planned to demonstrate a 50% reduction in infections and if *S. aureus* nasal carriage rates were about 25% then an adequately powered study in a population in which the no intervention clinical infection rate was only 2% would require around 26,000 patients. In addition, as infection control methods improve, the clinical events that might be prevented would be expected to further decrease thus increasing the sample size that would be needed.

There is a need to consider how well-defined eradication could be assessed as a surrogate for a clinical benefit. At present it is unclear how this could be addressed.

Discussion

There are few data on the possible risk of clinical disease resulting from carriage of many organisms, including MDR Gram-negative bacteria and vancomycin-resistant enterococci in the gut.

There was support as well as concern expressed regarding indications for eradication of carriage of specific bacteria without a convincing link to a clinical benefit. Exposing a large population to an intervention that may not actually have a clinical benefit raises a lot of potential concerns, including the risk that the agent would enhance the selection of organisms with some types of resistance mechanisms. The rates of carriage are subject to many factors, such as infection control measures, and these interventions may suffice in some settings.

It is important not only to define eradication but also to conduct appropriate microbiological validation studies. Studies should examine the duration of eradication and how long this state should persist to achieve the desired/proposed benefit. For example if eradication is deemed to be required throughout a period of hospitalisation the range of time periods that might apply in any one clinical situation should be taken into account.

The draft revision of the guideline makes a possible exception for the use of literature to support a link to clinical benefit for eradication of *S. aureus* from the nose. There are other examples that should be considered such as eradication of *N. meningitidis* from the nasopharynx of persons in close contact with proven cases of disease, eradication of *S. pyogenes* to reduce the risk of post-streptococcal complications and the eradication of *H. pylori*. Another possible example would be use of oral treatment to eradicate and also prevent recurrences of *C. difficile*-associated diarrhoea.

Prior data and experience regarding selective gut decontamination are relevant. Past studies demonstrated that 50% of infections in neutropenic individuals were associated with organisms from

the gut that were not present when patients entered hospital. However, selective decontamination has not been consistently demonstrated to be beneficial and it does select for antibacterial resistance.

Session 5. Reflection of in-vitro and in-vivo activity in the SmPC

Regulatory consideration

The draft revised guidance proposes a considerable revision of the structure of section 5.1 of SmPCs for new antibacterial agents with regard to reflecting normally susceptible species, problems of resistance that may be encountered in the EU and the demonstration of clinical activity against specific genera or species. The revision proposes to discontinue the current tabulation of organisms relevant to the indications classified according to their likely susceptibility, since the data used to support this table may be unreliable, unrepresentative and of little or no relevance to individual prescribers when resistant organisms are not uniformly distributed between or even within EU Member States. The removal of the table means that an alternative approach is needed for identifying pathogens against which it is considered that clinical efficacy has been demonstrated and it is proposed to do this under indication-specific sub-headings. The section will continue to highlight possible resistance issues that may be encountered and this will be updated at intervals after first approval.

It was underlined that SmPCs do not include a description of the clinical efficacy studies unless there is a specific problem identified that needs highlighting, in which case this may appear in section 4.4 and/or 5.1 depending on the nature of the issue. All the details of clinical studies will continue to be provided in the European Public Assessment Report. There is no plan to change this approach although some comments were received that requested modification of this policy.

Discussion

There was support for removing the tabulation of organisms from section 5.1 and replacing this with sections along the lines proposed. The need to continue to describe reported problematic resistance issues within the EU was underlined. The omission of susceptibility test interpretive criteria for disk diffusion testing was agreed since there is a EU-recommended reference method only for MIC determinations.

Explanation of next steps

The IDWP will consider the written comments received during the consultation period and the discussion during the Workshop. It is intended that the revision will be reviewed by the Guideline Consistency Group, before being finalised for adoption by CHMP during the second quarter of 2011.

If the IDWP decides that it would be useful to develop an addendum in which more detailed consideration would be given to individual indications (noting that this approach has already been taken with respect to new agents to treat tuberculosis) then this would require agreement from the CHMP. In the first instance the IDWP would develop a Concept Paper and propose this to CHMP for adoption. Once a Concept Paper has been agreed, the development of such an addendum will proceed according to the agreed timetable.