NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of pseudomonas lung infection in cystic fibrosis

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Personal background

I have provided consultant medical supervision of adult cystic fibrosis patients since 1987, and was the principal clinician involved in setting up the Scottish National Adult Cystic Fibrosis Service in 1992. I also have substantial experience in inhalation technologies, dating back to research work in the late 1970's, concerning mucociliary clearance, and subsequently with inhalation devices primarily for asthma management, but also for delivery of inhaled insulin.
I have been a consultant Respiratory Physician since 1984, with honorary University appointments, including an honorary chair since 2003. I am a member of the Association of Physicians, the American Thoracic Society, and the European Respiratory Society, was President of the Scottish Thoracic Society 2008-10, and am current President of the British Thoracic Society.

Comment on the drugs under consideration

Colistimethate sodium and tobramycin have been use in the management of cystic fibrosis for many years. Both drugs are used by intravenous administration, usually in the management of acute exacerbations of cystic fibrosis lung disease, and both are administered by the inhaled route via nebuliser, either in relatively short term therapy as part of eradication programmes to try to clear *Pseudomonas aeruginosa* from the airways of patients on its first (or recurrent) appearance, or more commonly on a long term basis to try to reduce the exacerbation frequency of patients who are permanently colonised by *Pseudomonas aeruginosa*.
The current agents being assessed are these drugs but administered as dry powder via dry powder inhalation devices. While authorities in the UK consider drug + device as a key component, we should recognise that we are discussing no new drug, but simply considering established drugs delivered by a different inhalational system. Thus, the first question I would ask myself, as a clinician, is "is the dry powder formulation + device as effective and safe as the existing formulation + nebuliser". I am disappointed that Forest Laboratories have not provided any evidence in that regard, and I make the presumption that they chose to examine colistimethate sodium DPI against nebulised tobramycin since that might allow them to set a price against nebulised tobramycin rather than against their own product of nebulised colomycin, which is substantially cheaper.

Comment on the dry powder inhalation devices and nebulisers

There is little doubt in my mind that a number of patients would be very pleased to have the opportunity to take their antibiotic via an easy-to-use inhaler rather than a nebuliser. Both dry powder devices are easy-to-use, with the Novartis device being less convenient since 4 capsules per dosing are required rather than one. (I was, however, unable to see the data from

both companies that justified the doses chosen). Both devices have similar applications of technology and in truth one can see their origins in a dry powder device used in asthma management over 40 years ago. The devices are easy to use, and have benefits of portability and in cleaning. An important question is whether the dry powder inhalation causes adverse effects, and both companies provided information that suggested there was a substantial incidence of cough with the DPIs. This unwanted effect contributed to the higher drop-out rates in the clinical trials. What is not clear is whether, in the "real world" (i.e. not in the context of a clinical trial) this might lead to poorer patient adherence.

The nebuliser both companies chose for comparison with their DPIs was the licensed PARI LC plus. This is the nebuliser with which nebulised tobramycin was initially studied and approved. It is not the nebuliser that is necessarily used on a wide clinical basis in the UK. Many patients are taking treatment via alternative devices based on a different technology, such as the e-flow, which is silent, can be held in the palm of a hand, and delivers the drug in approximately 3 minutes. As such the potential advantage of a DPI system over the nebulised device is diminished with regards delivery time and portability. Although Novartis argue that tobramycin delivered by a device such as the e-flow cannot be assumed to be as effective as the trialled PARI system, the fact that the e-flow is used widely by clinicians would suggest that their argument is (? deliberately) "purist" since clinicians would not provide such therapy to their patients if it was clinically ineffective. For nebulised colomycin there is an approved device of similar efficacy to the e-flow, the i-neb, which is widely used, and many clinicians also use the e-flow for delivery of colomycin.

One is well aware that product licences reflect the application to the authorities by pharmaceutical companies, and this can lead to clinically effective therapy having to be administered "off-licence" because of the restrictive nature of the initial product licence application. In the current applications, in my opinion, some of the potential advantages of the DPI systems are overstated because of the restricted choice of nebuliser delivery system used.

Clinical trial endpoints

Both companies present clinical trial data that use the FEV_1 as an endpoint. The Assessment Group highlight that this has its limitations when trying to conclude longer term clinical benefits. I agree with the Assessment Group. FEV_1 is chosen as a primary outcome variable in many trials because this is what the regulatory authorities "demand". It is not the most informative for long term outcomes in cystic fibrosis. Respiratory exacerbations and health status are arguably more informative (indeed a reduction in exacerbation frequency and improved health status are what most clinicians are trying to achieve when employing long term inhaled antibiotic therapy). While there is an association between FEV_1 and mortality, this is a population observation with wide variation within. Thus the median survival of c.2y from a position of FEV_1 25 % predicted is what it says, "median" (i.e. there is a skew distribution). In addition the data that identified this are now quite old, and the figures would be less certain currently.

Clinical trial design

Trial design is critical for adequate interpretation of data. It is perfectly possible to influence outcomes simply by items in the trial design. In this regard, the clinical trial data from both companies employ an "open-label" design. I can understand this, since I presume that there

are no adequate placebo powder capsules (otherwise one would have expected a double-blind design). Nevertheless, we should be aware of the limitations of open-label when looking at outcomes, particularly patient preferences, quality of life (health status), and physician global assessment since these may be influenced by perceptions of "something new".

With regards the individual companies' presented clinical trials there are issues which I would like to consider. For both products, I can understand why the trial is only 24 weeks, but this short time does limit the ability to assess long term gains.

The data supplied by Forest Laboratories give me considerable concern. Their evidence really hinges around the COLO/DPI/02/06 trial, where DPI colistimethate sodium is compared with nebulised tobramycin. However, I have to ask why they have provided no data of comparison with their own nebulised product, which to me would be the correct first comparison. Could this be because they wished to use the trial to set the price for the DPI?? I would have wished also to see the evidence for the justification of the chosen DPI dose. My interpretation of the COLO/DPI/02/06 trial is that it is intrinsically flawed in design. (I observe that the trial has not been published in a peer reviewed publication, which is very surprising. Is this because it has never been submitted [if so why not?] or because referees have rejected it?). For a correct comparison between the two drugs there should have been no "run-in period on tobramycin, or selection of patients who were already taking it. First this favours tobramycin to the extent that it selects out patients who are unable to tolerate it, but more importantly, and in the opposite direction, it compares a new intervention with established therapy, and any "new intervention" would be expected to have an initial increased benefit (an argument that Forest themselves employ, in fact, to justify their approach to tobramycin). Both interventions should have had the same starting point, and ideally in patients naïve to both drugs, but at least in a balanced selection with regards prior use of either.
I would be concerned that any attempt at a cost-effectiveness comparison between the drugs is untenable if the study design is flawed in this way.

The data provided by Novartis are somewhat more reassuring in that the trial data have gone through a peer review process. The primary endpoint of the Eager trial was slightly unusual in that it was the incidence of adverse events (which indicates to me that the company was anticipating equality in more conventional endpoints). Although the patients expressed a preference for the podhaler, I have suggested the limitations of this as an endpoint with this study design. And there were substantially more trial withdrawls in the podhaler group as well as an increased incidence of cough.
Although the comparison between DPI and nebuliser tobramycin is fair, the absence of an alternative limb of treatment (e.g. oral macrolide) limits the assessment of cost-effectiveness since the baseline comparator of nebulised tobramycin has its price fixed, and therefore there is no comparison of efficacy with a cheaper alternative.

Conclusion

It is nice to see alternative delivery systems for established therapies that at present can only be delivered by nebuliser. The drug delivery systems do not appear to reveal themselves as a standard of inhaler – they appear more like older, less satisfactory DPIs. However, I appreciate that there will have been substantial work to develop the dry powder formulation and stability of the drugs.

I was disappointed in the amount and quality of supporting clinical data to justify the proposed drug expenditures, and on balance I do not think the delivery systems are so effective that I will see a driving force to make me want to change patients over from their nebulised therapy.

While the data provided on behalf of DPI tobramycin appear sufficient for it to be seen as an alternative to nebulised tobramycin, I was very disappointed by the supporting data for colistimethate sodium DPI. There was no evidence to show a comparison with nebulised colistimethate sodium (which would have one level of relative cost), and I believe the trial to compare with nebulised tobramycin was sufficiently flawed methodologically that data from it do not justify the cost-effectiveness comparisons.