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Clinical Trial Reports, how reliable?

We tend to believe what we read in the peer-reviewed literature. Should we? Are we reading the proverbial whole truth and nothing but..? Should we be worried? Recent reports make one uncomfortable. Instances: a story of the publication of an important epoetin trial by a prominent peer-reviewed journal in 1998 which proclaimed benefits of raising hematocrit levels above 30 with that drug in patients on long-term renal dialysis (1). The trial was terminated prematurely because of a trend towards increased deaths and heart attacks with higher doses of the drug. Not reported, however, was that the statistics had been adjusted in a manner that showed only a trend and not a statistically significant safety concern. The raw, unfavorable unadjusted statistics were not reported in the publication. Following this report, the National Kidney Foundation Guidelines recommended epoetin dosages to maintain higher hematocrit levels because of better "physical function" and fewer transfusions. The use of epoetin exploded.

The serious adverse events associated with higher dosages of epoetin have since become clear, -more cardiovascular, cerebrovascular, and thrombotic events, and higher all-cause mortality.

The original trial data were never independently reviewed. Only some 14 years later and then only after invoking the Freedom of Information Act, did independent analysis reveal that the data filed with the FDA "shows that bigger doses of epoetin to target higher hematocrit did not improve physical function quality of life at all, and had significantly increased the risk of death, heart attack, other thrombotic events, and hospitalizations" (2, 3). The transfusion benefit was minor in comparison with the substantial cost and number needed to treat, and, of-course, the serious adverse event rate.

Perhaps if the trial data had been made available for independent review at the time of the initial publication, the shortcomings of the report would have been revealed much earlier. One wonders to what extent the authors of the report themselves were provided with all the data by the sponsors.

Another very recent report: the H1N1 influenza pandemic of 2009 infected tens of millions of patients and killed more than 10,000. Successive waves of the disease were feared and millions of doses of the antiviral agent, Tamiflu, were released from stockpiles. There was a general belief that the use of Tamiflu could moderate the severity of pneumonia and other serious consequences of 'flu' infections. However, when the outcomes of further studies were independently reviewed at the time of the 2009 flu pandemic, it was found that neuraminidase inhibitors, including Tamiflu, did not reduce the complications of influenza (4). This was apparently because the Cochrane Collaboration that commissioned the independent study had rejected the positive results of 8 trials that had been included in the original report but that had never been published. The sponsors of Tamiflu, Roche, to their

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credit, were willing to provide all the raw trial data to the Cochrane investigators.

The investigators found problems with the unreported trials such as mismatched active treatment and placebo groups, the absence of a standard definition of pneumonia, and that influenza-like events that lacked laboratory-confirmed influenza had been included (5).

Other examples of the concealment of trial data problems, deliberate or inadvertent, that can misrepresent or obscure the real outcome of a clinical trial are provided (6).

As journal-reading physicians we tend to rely on the peer-review process to eliminate uncertainty. We have very little concept that a 6 page article in the most prestigious journal is a distillation of possibly 10,000 pages of raw data. The FDA receives far more information than it ever makes available for independent scrutiny. For the Agency, there is the issue of the confidentiality of proprietary information. For the pharmaceutical company that owns the data and offers its trial results to investigators to publish, who decides what and how much is shown to the authors? When the paper is submitted for publication, how critical is the review process? Meta-analyses by their nature constitute yet another layer of uncertainty. The assumption that one can collect a market basket of diverse trials and *ipso facto* knit them into something new and revelatory is probably naïve. Condensing all the problems of several trials into one hard-to-understand data-set is as likely to conceal all the flaws and arbitrary data selections of its components is as it is to reveal a previously obscure truth, -not unlike the slicing and dicing of credit-default swaps and other creative legerdemain that are incomprehensible even to financial professionals. In a few words: be skeptical and very critical.

ULABA-ULAMA Combinations Combivent, Boehringer-Ingelheim's albuterol-ipratropium combination MDI, has been one of the most widely used drugs for symptom relief in COPD since its approval. But, being a combination of short-acting agents, Combivent lacks many of the patient-centered benefits that can be obtained with long-acting bronchodilators. The same can be said for DuoNeb, Dey/Mylan's nebulized version of the same 2 agents. Thus, since long-acting agents of both classes of bronchodilators have become available, pulmonologists, PCP's and patients have been wondering when long-acting versions of Combivent would become available.

At present at least 3 ULABA-ULAMA combinations are working their bumpy way towards approval. GlaxoSmithKline has the combination of 573719, a ULAMA, with their ULABA, Vilanterol. GSK573719 has been in 21 trials, 9 of them in Phase III. All but one of these has been in a combination with Vilanterol. The pivotal Phase III trials of the combination include 2 doses of the ULAMA, 62.5 and 125 mcg together with 25 mcg of Vilanterol, delivered as a dry powder through a 'Novel' device.

Novartis has developed glycopyrrolate, renamed glycopyrronium NVA237, as their ULAMA. The molecule is well known having been developed in the 1960's as an antispasmodic for peptic ulcer disease, and it is still in continuous use in anesthesiology. Thus, it has an extensive safety record. (The same molecule, being long-off patent, is the LAMA being developed as a monotherapy or in a b.i.d. combination by several other pharmaceutical companies). Compared to tiotropium, the first ULAMA to be approved, glycopyrronium has a more rapid onset of action but a slightly shorter duration of action. Novartis's combination is with their ULABA indacaterol or QAB149, recently approved as a monotherapy and now known as Arcapta. The combination, QVA149, has been in several phase III studies, early reports of which are available by press releases, http://www.novartis.com/newsroom/media-releases/en/2012/1599186.shtml. The eventual dose of its indacaterol component is unclear at present, so its FDA approval may be delayed substantially.

Boehringer-Ingelheim is developing a combination of their ULAMA agent tiotropium with a novel ULABA, olodaterol, BI1744. Olodaterol is a full agonist, highly selective for beta$_2$ adrenergic receptors with both rapid onset and long duration of bronchodilation (8). Like the rest of Boehringer's respiratory portfolio, the intention was to market the combination with the Respimat delivery device. However, safety concerns about Respimat have been raised by a meta-analysis of tiotropium/Respimat use in Europe that showed a 46% increase in all-cause mortality in patients receiving 5 mcg tiotropium by Respimat versus placebo (9). (A higher dose, 10 mcg, had approximately twice the mortality and has since been withdrawn). Although the meta-analysis has been considered to be robust, we have been misled by meta-analyses in the past. To resolve the issue of Respimat safety a 2-year head-to-head study is ongoing (not presently listed in clinicaltrials.gov). Until its completion, it is unlikely that the tiotropium-olodaterol combination will go forward. The combination has been the subject of 11 clinical trials, every one of them using the Respimat delivery system.

One expects that each of the above 3 combination agents will be safe and very effective. It is hard to predict which of them will be approved first.

There are a number of twice-daily LABA-LAMA combinations in development stages, many of which combine glycopyrrolate with formoterol, but these will be reviewed in a future "Pipeline". Also being considered are a couple of long-acting combinations that will be delivered by nebulization.

Advances in Anti-Inflammatories for COPD

Mesenchymal Stem Cells, I reported on the Osiris Therapeutics-sponsored mesenchymal stem cell trial for emphysema Prochymal, in a previous Pipeline (7). Another study of stem cells for the same purpose is being

conducted by Leiden University Medical Center. The interesting design recruits candidates with advanced emphysema for bilateral lung volume reduction surgery, LVRS, in 2 stages. Following unilateral LVRS, subjects will receive 2 infusions of autologous mesenchymal stem cells a week apart and receive LVRS on the contralateral side 3 weeks after the second infusion. The primary outcome will be safety endpoints, but one presumes (and hopes) the 2 lung resections will be compared for evidence of parenchymal repair (NCT01306513).

NovImmune is a small Swiss biotech company whose focus is on developing therapeutic monoclonal antibodies which target inflammatory diseases and immune-related disorders. To date, NovImmune has generated seven proprietary monoclonals, http://novimmune.com/ . Those that may be of interest for COPD inflammation and their molecular targets are: NI-0401 vs CD3e in Phase I; NI-0101 vs TLR4 in preclinical; NI-1401 vs IL-17 in preclinical and NI-1201 vs IL-6R in preclinical.

FX125L This is the lead product-in-development of Funxional, a biotech company headquartered in Cambridge England, whose plan is to develop somatotaxins, or somatostatins. Unlike naturally occurring somatostatins, which are proteins, somatotaxins are small molecules and orally-active and have a wide therapeutic margin. They exhibit broad anti-inflammatory actions through the type-2 somatostatin receptor, SSTR2. Their efficacy has been demonstrated in a broad range of animal models, including asthma and COPD, diabetic nephropathy, and rheumatoid arthritis. Their eventual clinical potential and most appropriate targets remain to be identified. FX125L has now successfully completed a phase I safety trial. Present evidence suggests they will be safer than corticosteroids and might be active in conditions for which corticosteroids have little efficacy.

AUF1 On a more distant horizon is AUF1, a family of 4 genes that appears to be the key link between inflammation, cell senescence and telomere maintenance (10). AUF1 activates telomerase expression, suppressing cell senescence and maintaining normal ageing. AUF1-knockout mice age rapidly, a process that can be rescued by resupplying AUF1. A new study shows, surprisingly, that the same gene also suppresses inflammation by directing the decay of inflammatory cytokine mRNA.

It has long been known that inflammation and aging are somehow linked. Indeed COPD has been referred to as a disease of premature aging. Now, in the words of Robert Schneider, the lead investigator of this NYU study, *"Nature has designed a way to simultaneously turn off harmful inflammation and repair our chromosomes, thereby suppressing aging at the cellular level and in the whole animal."* Could an inducer of AUF1 be the anti-inflammatory agent we need for COPD?

COPD Biomarkers

A new series of columns on COPD Biomarkers will be published in the Journal beginning with the August 2012 issue. The series will be edited by Steve Rennard and Gerry Turino will author the first of the series.

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Declaration of Interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of this paper.

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