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CLINICAL INVESTIGATION

News

Highlights from the latest news and research in Clinical Investigation

Study results suggest increasing disclosure in industry-sponsored clinical studies

Concerns have long prevailed regarding the transparency of data reporting in medical trials funded by pharmaceutical manufacturers. In order to examine the reporting level of these studies a recently published clinical trial has examined clinical trial registries and regulatory agency information within the EU to discern what proportion of clinical studies make results public. The study, funded by the Association of the British Pharmaceutical Industry (ABPI) and published in *Current Medical Research and Opinion*, has suggested that reporting levels may be somewhat higher than previously believed and that the proportion of trials reporting results over a recent 3-year period is increasing.

The study team surveyed a variety of public information sources for both trial registration and presentation of results. The information resources used included clinical trial registries, the International Federation of Pharmaceutical Manufacturers and Associations' Clinical Trials Portal, European Medicines Agency European Public Assessment Reports and PubMed. The years included in the study were 2009, 2010 and 2011, and included all completed manufacturer-sponsored trials that were conducted in patients, recorded on a clinical trial registry, and those included in the European Medicines Agency European Public Assessment Reports. The study did not include vaccines and fixed-dose combinations of medicines and identified 53 newly approved pharmaceuticals manufactured by 34 companies.

The primary outcome measure included in the research was the proportion of the clinical trials conducted that had some results disclosed, either in a registry or the scientific literature within 12 months following trial completion or regulatory approval, whichever was later; the proportion of studies reporting by the end of the study period (ending 31 January 2013) was also included in the analysis.

The results showed that, of clinical trials conducted on the 53 medicines approved during the period concerned in the study, 77% of the trials had results reported within 12 months of European Medicines Agency approval. When reporting was extended to January 2013, the proportion of studies reporting increased to 89%. When the approval of medication and trial completion were examined on a year-by-year basis for 2009, 2010 and 2011, it was found that 71, 81 and 86% of trials reported within 12 months, respectively; this increased to 86, 93 and 91%, respectively, when reporting by January 2013 was the accepted criteria.

While the rates of data reporting were high and suggest an increase in result reporting from manufacturer-backed trials, with greater than three-quarters of studies reporting within 12 months and nearly nine in ten studies reporting by the end of January 2013, the trial did include some limitations. The strictly quantitative nature of the study meant that there were no criteria for quality or extent of reporting; as long as some data were reported, a trial was considered to have provided data, meaning that the degree of transparency could vary hugely between clinical trials included in the study.

Discussing the study's results and implications, ABPI Chief Executive Stephen

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Whitehead highlighted the positive upward trend; while concluding that the study should serve as a starting point, with work to increase transparency further following, commenting, "The ABPI is a strong advocate for transparency in clinical trial data, so it is encouraging to see a distinct upward trend towards even greater disclosure of results in industry-sponsored trials. However, more can be done to achieve even greater transparency. There are no quick fixes to this global issue, but this research provides an important baseline that identifies where there is still work to be done … This study marks an important step, and we fully expect to see the trend towards greater transparency continue on this positive trajectory."

–Written by Sean Fitzpatrick

Sources: Rawal B, Deane BR. Clinical trial transparency: an assessment of the disclosure of results of company-sponsored trials associated with new medicines approved recently in Europe. *Curr. Med. Res. Opin.* DOI: 10.1185/03007995.2013.860371 (2013) (Epub ahead of print); The Association of the British Pharmaceutical Industry: www.abpi.org.uk/media-centre/newsreleases/2013/Pages/11112013a.aspx

Hyperkalemia drug demonstrates positive results in Phase III study

Positive topline results of the anti-hyperkalemia drug, investigational name ZS-9, have recently been reported. Manufacturer, ZS Pharma (Coppell, TX, USA) said the results of the pivotal Phase III study, named ZS-003, demonstrated safety and efficacy and stated that the trial had met its primary endpoint, significantly reducing serum potassium in 48 h.

The trial was a randomized, placebo-controlled, double-blind trial and enrolled a total of 753 subjects with hyperkalemia. Following randomization, patients received either ZS-9 at one of four doses or placebo. During the initial 48-hour acute phase of the trial, patients received treatment three-times daily. Patients that normalized during this phase of the trial were then randomized again to receive one of four doses of study drug or placebo once daily for 12 days in the subacute phase of the trial. The primary endpoint examining serum potassium reduction during the acute phase was the same as that used in the previous, first-in-man, proof-of-concept ZS-002 trial of ZS-9. The ZS-003 trial included a secondary endpoint looking at the change in serum potassium during the 12-day subacute phase.

The results of the acute phase were reported by Stephen R Ash of Indiana University Health Arnett (Lafayette, IN, USA) at the American Society of Nephrology's Kidney Week. The trial met the primary efficacy endpoint for the highest three doses of ZS-9. It was also found that ZS-9 was well tolerated by the trial participants, with an adverse event rate similar to that of placebo. Commenting on the trial results, Ash said, "Hyperkalemia is a serious medical condition associated with significantly increased mortality rates, but physicians lack a safe and reliable therapy to lower serum K+ level. ZS-9 shows promise as an effective, well tolerated, fast-acting, and predictable treatment for patients with hyperkalemia."

Further results from the trial, including the results of the subacute phase are expected to be announced in the coming months. Highlighting the promise of the early results achieved so far, Geoff Block, director of clinical research at Denver Nephrology, associate clinical professor in medicine at the University of Colorado Health Sciences Center and a clinical investigator in the ZS-003 study, said, "The preliminary Phase III study results are promising and I look forward to additional Phase III results as they become available … There is a critical need for a new treatment for patients with hyperkalemia, including those with chronic kidney disease, diabetes, heart failure and those who should be on cardio-renal protective treatment such as ACEs and ARBs."

–Written by Sean Fitzpatrick

Source: ZS Pharma: www.zspharma.com/downloads/ZS_Pharma_Announces_Positive_Top-Line_Results_of_Phase_3_Trial_of_ZS-9_in_Patients_with_Hyperkalemia.pdf

An enzyme may be the future for preventing cancer growth and relapse

A team of investigators led by Dmitry Bulavin (Agency for Science, Technology and Research, Singapore) have built upon previous research that uncovered an enzyme, Wip1 phosphatase, to be involved in regulating tumor growth. The findings, published online in the October issue of *Cancer Cell*, uncovered Wip1 phasphatase's mechanism of action, which may lead to the more effective prevention of cancers and reduce the chance of relapse.

Bulavin comments, "Our work on Wip1 phosphatase for over a decade has now revealed several key features of this molecule. Our current findings strongly support the use of an anti-Wip1 drug for cancer treatment in order to reduce a high frequency of mutations in the genome, which is one of the main drivers of tumor relapses."

The research demonstrated that this enzyme causes point mutations leading to the 'spouting' of human cancer. These mutations originate from DNA replication errors in the body causing alterations in one base-pair. This leads to the increased resilience of cancers as they 'take root' in the body. Drugs that could potentially inhibit Wip1 phosphatase could therefore stop tumor growth and may mean that the cancer is less likely to develop resistance to treatment.

Director of the Agency for Science, Technology and Research's Institute of Molecular and Cell Biology, Hong Wan Jin, concludes, "Dmitry has been

the pioneering driver in the mechanistic study of Wip1 phosphatase, and this discovery is monumental in providing novel understanding on the role of Wip1 in cancer at the genomic and systems levels. I am confident that his team at Research's Institute of Molecular and Cell Biology can further their work in cancer research to offer new approaches for potential drugs against this target."

– Written by Elizabeth Webb

Source: Agency for Science, Technology and Research press release: www.a-star.edu.sg/Media/News/Press-Releases/articleType/ArticleView/articleId/1908.aspx

New drug reduces need for alternative anemia therapy in chronic kidney disease

Presented at the American Society of Nephrology Kidney Week in Atlanta, Georgia (USA) the results of the FIND-CKD study demonstrate that Ferinject® (Vifor Pharma, Glattbrugg, Germany) significantly reduces or delays the need for alternative anemia management in non-dialysis-dependent chronic kidney disease (ND-CKD). Alternative anemia management is frequently required for patients on existing oral iron therapy.

Ferinject also stimulates a faster hemoglobin response, with a larger proportion of patients achieving a hemoglobin increase greater than 1 g/dl. Intravenous Ferinject was also demonstrated to be well tolerated with fewer treatment-related adverse events and discontinuations when compared with oral iron therapy.

"The question of whether intravenous iron therapy is an appropriate first-line therapy in patients with ND-CKD is currently an issue of intense debate. FIND-CKD is the largest and longest study of intravenous versus oral iron therapy without erythropoiesis-stimulating agents in this patient population. It is also the first such trial that uses requirement for alternative anemia management as the primary endpoint rather than hemoglobin. While the FIND-CKD study achieved its primary endpoint and is of importance to clinicians who treat patients with ND-CKD, I believe that the findings could have wider implications for the management of iron deficiency anemia in other settings such as surgery, gynecology and oncology," commented Iain Macdougall of King's College Hospital (London, UK).

FIND-CKD is the largest and longest prospective, randomized clinical trial ever conducted comparing intravenous versus oral iron for the treatment of iron deficiency anemia in patients with ND-CKD who were not receiving erythropoiesis-stimulating agent therapy. More than 600 patients from 20 countries were included in this 56-week clinical study. Patients were randomized to receive Ferinject targeting a higher (400–600 ug/l) or lower (100–200 ug/l) serum ferritin level, or oral iron. The study met its primary endpoint, demonstrating that Ferinject given at a starting dose of 1,000 mg with subsequent dosing as required to maintain a serum ferritin of 400–600 ug/l significantly reduced or delayed the need for alternative anemia management or the occurrence of two consecutive hemoglobin levels <10 g/dl compared with oral iron. These results were achieved with in average four Ferinject injections.

To date there have not been sufficiently large and long trials investigating the relative efficacy and safety of intravenous versus oral iron therapy, and iron therapy based on different serum ferritin targets has not been previously studied. These data demonstrate that treatment with Ferinject targeting a higher serum ferritin level is an effective, well-tolerated and convenient therapy for iron deficiency anemia in patients with ND-CKD, and may improve and simplify the quality of care in these patients.

– Written by Adam Born

Source: Vifor Pharma. Press Release. Ferinject® reduces or delays requirement for alternative anaemia management compared with oral iron therapy: FIND-CKD study presented at the American Society of Nephrology (ASN) Kidney Week (2013): www.viforpharma.com/en/Media/mediareleases/2013/20131111_find-ckd-131111.php

Long-term study results address the use of perioperative chemotherapy for initially resectable liver metastases

Perioperative chemotherapy with folinic acid, fluorouracil, and oxaliplatin (FOLFOX4) has no significant effect on overall survival compared with surgery alone for patients with resectable liver metastases from colorectal cancer. This was the conclusion reached by the long-term, recently reported, European Organisation for Research and Treatment of Cancer Phase III intergroup trial 40983.

Despite this, authors still recommend that perioperative FOLFOX4 chemotherapy should remain the reference treatment for this population of patients, owing to their earlier findings from the same trial that administration of perioperative FOLFOX4 increases progression-free survival, the primary endpoint, compared with surgery alone. Furthermore, as overall survival was a secondary endpoint, the trial was not initially powered to compare overall survival in the two groups.

"Surgery is currently the only potentially curative treatment for resectable liver metastases, yet only 15–20% of patients with hepatic metastases are initially eligible for a radical surgical treatment," explained lead author Bernard Nordlinger (Université de Versailles, Boulogne-Billancourt, France). "Furthermore, less than one half of patients who do receive such treatment achieve 5-year survival after resection. This is likely due to the presence of residual disease, so it is thought that adjuvant chemotherapy could help these patients."

The study was conducted between October 2000 and July 2004, during which a total of 364 patients, aged 18–80 years of age, were recruited from 78 hospitals in 11 countries across Europe, Australia and Hong Kong. All patients had histologically proven colorectal cancer and up to four hepatic metastases. Patients were then randomly assigned (1:1) to either perioperative FOLFOX4 or surgery alone.

At a median follow-up of 5–8 years (interquartile range 7.6–9.5 years), 59 versus 63% of patients had died when treated with perioperative chemotherapy compared with surgery alone, respectively. This trial is registered with ClinicalTrials.gov (NCT00006479).

– Written by Emma Sinclair

Sources: Nordlinger B, Sorbye H, Glimelius B *et al.* Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol.* 14(12), 1208–15 (2013); Press release: www.eortc.org/news/long-term-results-eortc-trial-patients-resectable-liver-metastases-colorectal-cancer

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