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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in clinical investigation

Clinical trial identifies potential new treatments for infantile eczema

The results of a recent clinical trial report the safe and effective treatment of infantile eczema using a topical Lipoxin A_4 analog cream.

A recent trial conducted by researchers at the First Affiliated Hospital of Nanjing Medical University (Jiangsu, China) and the Hospital of Southeast University (Nanjing, Jiangsu, China) has identified a potentially effective drug treatment for infantile eczema. The trial measured the ability of Lipoxin A_4 analog cream, consisting of 15(R/S)-Methyl-Lipoxin A_4, for efficacy and safety in topical treatment of infantile eczema. The effectiveness of the topical drug was reported recently in the *British Journal of Dermatology* to be similar to that of a commercially available corticosteroid cream, and could potentially open the door to new treatments for infantile eczema in the future.

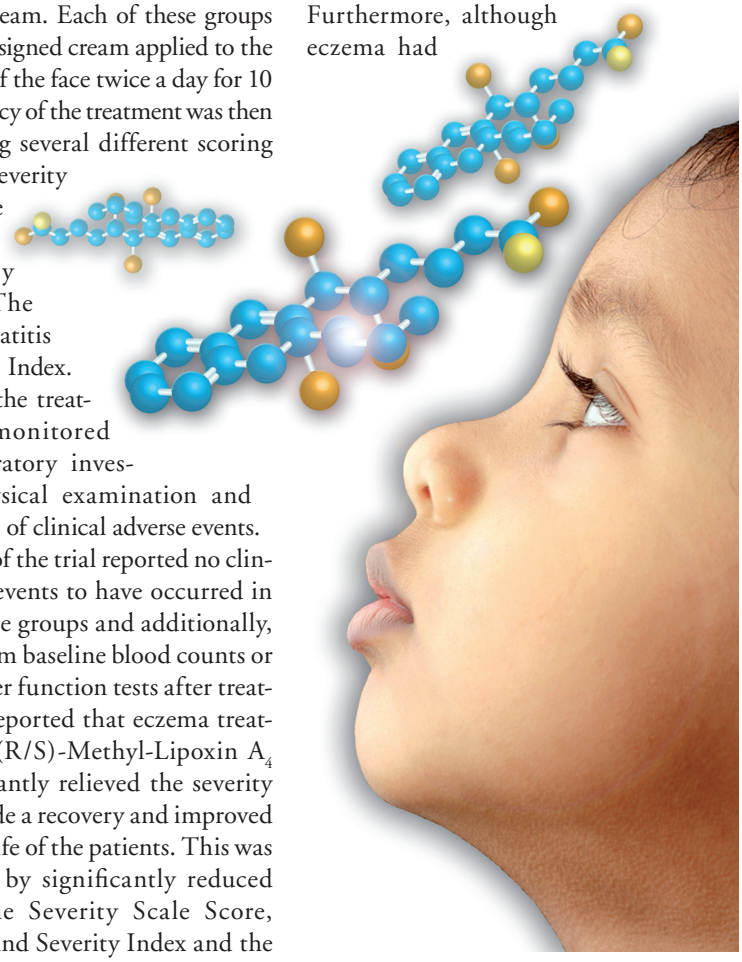
Lipoxins, which make up the new topical drug, are non-classic eicosanoids. Evidence accumulated from the use of Lipoxin A_4 (and its analogs) in the treatment of animal models of inflammatory diseases have indicated Lipoxins as potential anti-inflammatory mediators as they are thought to serve as an endogenous 'braking signal' in the inflammatory process. Although originally tested decades previously in humans as an inhaled asthma treatment, the current trial is the first clinical study of a topical Lipoxin A_4 analog.

Prior to the trial, the hospital conducted safety tests on the Lipoxin A_4 analog cream. First, the cream was made up containing 15(R/S)-Methyl-Lipoxin A_4 in the drug preparation centre of the hospital. The drug was then tested on the facial skin of an adult doctor to test for discomfort. After no discomfort originated after a 10-day application period, a secondary safety test, consisting of a pilot study in two infants, was performed. The main trial was then conducted following on from no contraindication by these safety measures.

Two centers were involved in the trial, which followed a double-blind, placebo-controlled, randomized, parallel-group comparative study method. The trial consisted of 60 infants suffering from eczema, ranging in age from 1 month to 1 year. These 60 patients were then enrolled and randomly assigned to receive either the measured 15(R/S)-Methyl-Lipoxin A_4 cream, a 0.1 percent mometasone furoate cream (known in China as Eloson™) or a placebo cream. Each of these groups then had the assigned cream applied to the affected areas of the face twice a day for 10 days. The efficacy of the treatment was then measured using several different scoring systems; the Severity Scale Score, the Eczema Area and Severity Index and The Infants' Dermatitis Quality of Life Index. The safety of the treatment was monitored through laboratory investigations, physical examination and documentation of clinical adverse events.

The results of the trial reported no clinically adverse events to have occurred in any of the three groups and additionally, no changes from baseline blood counts or kidney and liver function tests after treatment. It was reported that eczema treatment with 15(R/S)-Methyl-Lipoxin A_4 cream significantly relieved the severity of eczema, made a recovery and improved the quality of life of the patients. This was demonstrated by significantly reduced results for the Severity Scale Score, Eczema Area and Severity Index and the Infants' Dermatitis Quality of Life Index respectively, in a similar way to the efficacy of Eloson. It was documented that the 15(R/S)-Methyl-Lipoxin A_4 cream by day 3 reduced pruritis and scratching, by day 5 reduced papulation, vesiculation and scaling and by day 10 reduced lichenification. All of these symptoms were recorded to have also been reduced in the Eloson group by day 3, except for lichenification.

In addition to the immediate results of the trial, it was found that symptoms had not rebounded at day 17 of the study. Furthermore, although eczema had



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returned in 63% of the 15(R/S)-methyl-lipoxin A_4 group and 53% of the mometasone group at day 40, this was not found to be a statistically significant difference between the two groups. In the concluding remarks of the paper, the team write that "The results of this small exploratory study suggest that 15(R/S)-methyl-Lipoxin A_4 warrants further investigation in the treatment of eczema." Although studies with larger sample sizes will be needed before all side effects can be identified, this new clinical trial holds strong promise for a future treatment of infantile eczema.

– Written by Jenaid Rees

Source: Wu SH, Chen XQ, Liu B, Wu HJ, Dong L. Efficacy and safety of 15(R/S)-Methyl-Lipoxin A_4 in topical treatment of infantile eczema. *Br. J. Dermatol.* doi:10.1111/j.1365-2133.2012.11177.x (2012) (Epub ahead of print).

Clinical trials for antiretroviral therapies: exploring gender differences

A meta-analysis of data from antiretroviral trials in HIV-positive patients has explored potential gender differences in the efficacy of the therapy.

In a collaboration between the US FDA and the University of Texas Southwestern Medical Center (TX, USA), a group of researchers have presented their findings into gender differences in HIV trials. The team carried out a meta-analysis of trials from 2000–2008, presenting 'the most systematic review of gender-related antiretroviral therapy (ART) efficacy data to date'.

The meta-analysis was carried out using a database established by the FDA's Division of Antiviral Products, which contained information on 20,328 HIV-positive patients from 40 randomized-controlled trials. These trials were for 18 new drug applications – proving either the efficacy of a new molecule, or the efficacy of a new formulation or major label change of a current therapeutic. The included studies were at least 48 weeks in length.

The team elucidated the efficacy of these new drugs by looking at a common measure for antiretroviral therapy – less than 50 copies per milliliter of HIV RNA at 48 weeks. Women are often underrepresented in HIV trials, so determining whether there is a gender difference in response to ART can be difficult. Owing to the low numbers of females enrolled in these trials, analyses of gender-related data lack statistical power. In this meta-analysis, data from numerous trials could be pooled together to allow this group of patients to have statistical power.

The researchers discovered no statistically significant difference in outcome to ART between genders, and present these findings in a recent issue of *AIDS Patient Care and STDs*. In their conclusion, the team looks forward to future work, which: "includes investigating specific ARTs or ART regimens that may lead to the gender differences in outcome measurements. Other statistical modeling techniques such as Bayesian meta-analyses may be considered."

– Written by Alice O'Hare

Source: Soon G, Min M, Struble KA *et al.* Meta-analysis of gender differences in efficacy outcomes for HIV-positive subjects in randomized controlled clinical trials of antiretroviral therapy (2000–2008). *AIDS Patient Care STDS* 26(8), 444–453 (2012).

Phase II trial highlights that a nonoperative approach is feasible in advanced colon cancer

Results from the NSABP Trial C-10, a multicenter, prospective, Phase II trial, have highlighted that treating surgically unresectable metastatic colon cancer and an asymptomatic intact primary tumor patients with bevacizumab and infusional fluorouracil, leucovorin and oxaliplatin chemotherapy is a safe and viable option.

The trial enrolled 90 patients treated with infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus bevacizumab, without resection of the primary tumor, between March 2006 and June 2009. The primary end point was major morbidity events (25% major morbidity rate was considered acceptable) and secondary end points included overall survival and minor morbidity related to intact primary tumor (IPT) requiring hospitalization, transfusion or nonsurgical intervention.

In total, 86 patients were eligible with follow-up, with the median follow-up being 20.7 months. Median age was 58 years and 52% of participants were female. The results, published in the *Journal of Clinical Oncology*, were as following:

- Twelve patients (14%) had major morbidity related to IPT: ten required surgery (8 obstruction; 1 perforation; 1 abdominal pain) and two patients died;
- The 24-month cumulative incidence of major morbidity was 16.3% (95% CI: 7.6–25.1%);
- Eleven IPTs were resected without a morbidity event: eight for attempted cure and three for other reasons;
- Two patients had minor morbidity events only: one hospitalization and one nonsurgical intervention;
- Median overall survival was 19.9 months (95% CI: 15.0–27.2 months).

The authors stated that the trial met its primary endpoint. "Combining mFOLFOX6 with bevacizumab did not result in an unacceptable rate of obstruction, perforation, bleeding, or death related to IPT. Survival was not compromised," the authors concluded, "these patients can be spared initial noncurative resection of their asymptomatic IPT."

– Written by Ruth Williamson

Source: McCahill LE, Yothers G, Sharif S *et al.* Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10. *J. Clin. Oncol.* 30(26), 3223–3228 (2012).

Treatment for acute lymphoblastic leukemia approved by US FDA

In a recent press release, the US FDA have announced their approval of Marqibo® for the treatment of Philadelphia chromosome negative acute lymphoblastic leukemia.

The FDA has recently approved Marqibo, a vincristine sulfate liposome injection, for the treatment of patients with Philadelphia chromosome negative acute lymphoblastic leukemia. The approval was under the FDA's 'accelerated approval plan', which allows patients expedited access to a drug for a serious disease.

The therapeutic consists of the common anti-cancer drug vincristine, enveloped within a liposome, and is injected intravenously once-per-week. The treatment is approved for patients suffering from this form of acute lymphoblastic leukemia who have relapsed two or more times, or for whom their leukemia has progressed following two or more regimens of previous therapy.

The safety of this therapy was evaluated in two single-arm trials. A total of 83 patients received the treatment, and adverse side effects were monitored. The drug's efficacy was assessed in a single clinical trial with 65 patients. Efficacy was measured as complete remission, or complete remission with incomplete blood count recovery, and 15.4% patients achieved this outcome.

Marqibo is marketed by Talon Therapeutics (San Francisco, CA, USA). According to the FDA's accelerated approval plan, the company is now required to continue additional clinical studies to confirm both the safety and efficacy of their therapy.

– Written by Alice O'Hare

Source: US FDA Press Release; www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm315027.htm

The US FDA approves ziv-aflibercept for metastatic colorectal cancer

The US FDA has announced the approval of ziv-aflibercept (Zaltrap®) for use in combination with a FOLFIRI (folinic acid, fluorouracil and irinotecan) chemotherapy regimen, in order to treat adults with metastatic colorectal cancer (mCRC).

> "An improvement in median survival time was noted with the addition of Zaltrap to FOLFIRI, accompanied by an improvement in response rate and a delay in tumor progression and growth."

Ziv-aflibercept is an angiogenesis inhibitor, inhibiting the blood supply to tumors, intended for patients whose tumors are resistant to or progressed after an oxaliplatin-containing chemotherapy regimen. The safety and effectiveness of ziv-aflibercept has been evaluated in the VELOUR study, a randomized clinical study of 1226 patients with mCRC, which demonstrated that patients who were assigned to ziv-aflibercept plus FOLFIRI combination lived an average of 13.5 months, compared to an average of 12 months for those receiving FOLFIRI plus placebo. The progression-free survival for patients receiving the ziv-aflibercept plus FOLFIRI combination was 6.9 months compared with 4.7 months for those receiving FOLFIRI plus placebo.

Following the promising trial results, ziv-aflibercept has been approved by the FDA. "This approval demonstrates the benefits of adding a biological agent, Zaltrap, to a commonly used chemotherapy drug regimen, FOLFIRI," stated Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "An improvement in median survival time was noted with the addition of Zaltrap to FOLFIRI, accompanied by an improvement in response rate and a delay in tumor progression and growth."

Speaking about the implications of the approval, Marwan Fakih, Professor of Medicine at the University of Michigan, said that "by approving ziv-aflibercept, physicians have an additional angiogenesis-targeting agent to consider in the second-line treatment of mCRC, as the FDA had previously approved bevacizumab in the first and second-line treatment."

However, Fakih warned that "it is still too early to determine the full clinical implications of ziv-aflibercept approval." He continued by explaining that "while the addition of this agent in the second-line treatment of mCRC improved overall survival, the improvement was modest and the difference in median survival was less than 1.5 months." As such, "It will be essential to investigate and identify potential biomarkers that identify patients with tumors that are most likely to respond to this line of therapy," Fakih stated.

Fakih also explained that "it is unclear if ziv-aflibercept will hold any advantages over bevacizumab continuation in the second-line treatment of mCRC. A recent randomized second-line Phase III clinical trial (TML study) has demonstrated similar improvements in overall survival when bevacizumab was added

to chemotherapy following progression on first-line bevacizumab-based combinations."

The most common side effects observed in patients receiving ziv-aflibercept plus FOLFIRI were decreased white blood cell count, diarrhea, mouth ulcers, fatigue, high blood pressure, increased amount of protein in the urine, weight loss, decreased appetite, abdominal pain and headache.

Discussing the use of ziv-aflibercept in future settings, Fakih explained that "extrapolation to the first-line setting or third-line setting and beyond is not appropriate at this time. Furthermore, extrapolation to other backbones of chemotherapy is also inappropriate." He concluded by noting that "a randomized first-line Phase II clinical trial (AFFIRM study) of ziv-aflibercept plus FOLFOX versus FOLFOX failed to reach its primary end point of increased 1-year progression-free survival rate. Simply stated, ziv-aflibercept should only be used with FOLFIRI in the second-line treatment of mCRC."

– Written by Ruth Williamson

Source: US FDA Press Release: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm314372.htm

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