TUTOR	Luigi Ricciardiello

TITOLO DEL PROGETTO

STUDIO CLINICO RANDOMIZZATO CONTROLLATO IN DOPPIO CIECO SULL'EFFETTO, LA TOLLERABILITA' E LA SICUREZZA DELL'ACIDO EICOSAPENTAENOICO COME ACIDO GRASSO LIBERO IN PAZIENTI AFFETTI DA POLIPOSI ADENOMATOSA FAMILIARE

DESCRIZIONE DEL PROGETTO

Stato dell'Arte e Razionale (Background and hypothesis)

Familial Adenomatous Polyposis (FAP) is an inherited susceptibility to diffuse colorectal adenomas and colorectal carcinoma, occurring in close to 100% of unresected colons, and caused by a germline mutation in the APC gene located on the long arm of chromosome 5 (Kinzler et al 1996). To prevent cancer development, it is recommended that patients with FAP undergo colectomy with ileo-anal or ileo-rectal anastomosis (or colectomy and end-ileostomy) at a socially convenient time before polyp progression to malignancy and before the age of 25. Patients with the attenuated FAP phenotype, often associated with mutations at the 5' terminus (exon 4 and proximally) (Spiro et al 1993), have fewer polyps and may often delay colectomy.

Colectomy removes the bulk of the polyps in FAP, therefore significantly reducing the cancer risk, yet retains the native rectum in situ allowing a good functional outcome and avoiding stoma formation. Subsequent proctectomy is indicated when polyp burden is frequently high in the remaining rectum, if large highly dysplastic polyps occur, or if frank malignancy develops. Proctocolectomy also significantly reduces the cancer risk with the removal of the colon and rectum. A pouch fashioned from the terminal ileum can be created, and anastomosed to the anus. Routine endoscopic surveillance is also required with timings dependent on the extent of the disease, with polyp ablation as necessary.

It has been suggested that omega-3 PUFAs in fish oil can modulate the high levels of colonic-mucosal cell proliferation rates associated with sporadic colonic adenomas (Anti M et al 1994) and furthermore, work at St George's Hospital Medical School, London, has shown significant beneficial effects of cell proliferation and apoptosis rates on the colonic mucosa of patients with a history of colonic adenomas using a highly purified, form of EPA as the free fatty acid (Courtney et al 2005).

The effects of EPA-FFA on polyps have been investigated in the Multiple intestinal neoplasia (Min) mouse. Compared to Ctrl, EPA-FFA 2.5% and 5% dramatically repressed polyp formation (by 71.5% and 78.6%, respectively, $P < 0.0001$) and reduced polyp load (by 82.5% and 93.4%, respectively, $P < 0.0001$). Polyps <1mm were predominantly found in the 5% EPA-FFA treatment arm while those measuring 1-3 mm were more frequent in the Ctrl group ($P < 0.0001$). A chemoprevention trial in FAP patients has been conducted using the EPA-FFA gastro resistant capsules. This was a single-centre, double-blind, randomised, placebo-controlled study conducted in adult subjects with a confirmed diagnosis of FAP and previous colectomy with ileo-rectal anastomosis. In total, 58 subjects were randomised, 29 to the placebo group and 29 to the EPA treatment group. The study demonstrated a statistically significant reduction in number of polyps ($p=0.0046$ Full analysis set) in a focal area of the rectum following six months treatment with EPA compared to placebo. Statistically significant differences between the EPA treatment group and placebo group were found for percentage change in number of polyps, percentage change in total polyp diameter and global rectal polyp burden (as assessed by the expert review panel). Treatment with EPA resulted in an increase in rectal mucosal content of EPA and DPA relative to other fatty acids (West et al 2010).

Ipotesi (Hypothesis)

EPA-FFA has chemopreventive effects towards colorectal cancer in patients affected by Familial

Adenomatous Polyposis.

Obiettivi (Aims)

Primary Objective: To determine the efficacy of EPA-FFA gastro-resistant capsules in patients with FAP in reducing polypectomy (total number of polypectomies for polyps > 5 mm in the rectum conducted during the 24 months study period).

Secondary Objectives

- To evaluate the clinical disease progression.
- To evaluate the long-term safety and tolerability of EPA-FFA.
- Change in polyp number at 24 months assessed by blinded review of video records.
- Change in score on the InSiGHT Polyposis Staging System (IPSS) at 24 months.
- Number of subjects requiring surgical intervention (not including polypectomies).
- Total number of polypectomies (polyps > 5mm in the rectum) conducted at 6 months, 12 months, 18 months.
- Change in polyp number at 6 months, 12 months, 18 months assessed by blinded review of video records.
- Change in score on the InSiGHT Polyposis Staging System (IPSS) at 6 months, 12 months, 18 months.
- Time to surgical intervention (not including polypectomies).
- Change in score on the Spigelman Classification of Duodenal Polyposis at 24 months.
- Patient's Global Impression of Improvement (PGI-I) at Months 6, 12, 18 and 24.

Safety Endpoints

The safety analysis will be conducted in all randomised subjects receiving at least one dose.

- The number and proportion of subjects with AEs.
- The number of subjects requiring hospitalisation.
- Assessment of clinical laboratory parameters.

Metodi (Methods). For complete details please refer to the submitted and accepted protocol.

Subjects known to have a diagnosis of FAP, and attending a specialist clinic, will be contacted. Subjects expressing an interest in participating will be interviewed at their scheduled clinic appointment to explain the study in detail, and discuss the risks, benefits, goals and limitations of the study.

Screening:

Eligible subjects will provide written informed consent prior to any study specific procedures being conducted. Following the provision of written, informed consent, the subject's medical history especially that relating to FAP will be documented. Female subjects of child-bearing potential will undergo a urine pregnancy test. Following a physical examination, height, weight and checks on vital signs, the subjects will have blood samples drawn for routine haematology and biochemistry analyses. Subjects will be asked to provide details of any concomitant medications.

Subjects with confirmed diagnosis of FAP, compliance with the inclusion and exclusion criteria and providing written informed consent will be registered on the e-CRF to obtain a screening number.

Subjects will then undergo an endoscopy. A video record will be made of the endoscopic examination of the rectum which will be viewed in a spiral fashion to the anal verge. All polyps of > 5mm in the rectum will be removed where possible, a record will be made of the size, rationale for removal and location of any polyps prior to their removal, this is conducted after completion of the video record of the endoscopic examination. Polyps ≤ 5mm in the rectum should be left in place unless there are other clinical reasons deemed necessary for these to be removed in which case the rationale for removal should be documented. The subjects FAP

will be classified in accordance with the IPSS. The IPSS classification will be verified by the Polyp Video Scoring committee prior to randomisation.
Subjects compliance with the inclusion and exclusion criteria will be re-evaluated following endoscopy and eligible subjects will be randomised.
Subjects not wishing to participate, or who are ineligible, will be followed up in accordance with the clinic's standard management procedures.
Baseline/Randomisation:
Eligible subjects will be randomised on a 1:1 basis to one of the two treatment arms: EPA-FFA 500mg gastro-resistant capsules or matching Placebo gastro-resistant capsules.
Subjects will be provided with a supply of investigational medicinal product (IMP). Following the baseline visit subjects will administer IMP orally two capsules twice daily.
The subject will be trained on the completion of the diary and asked to record any changes in their condition or concomitant medication as relevant.
Telephone assessments to evaluate adverse events, compliance with study medication and details of any concomitant medications, will be made at week 1, then every second month from the date of randomisation until the 24-month visit. Any changes in health and concomitant medications must be registered in the e-CRF.
Visit Procedures (6 months, 12 months, 18 months):
Subjects will attend the clinic every 6 months. The diary will be reviewed to ensure completion of the diary and to check for any changes in their condition or concomitant medication. Any changes in health and concomitant medications must be registered in the e-CRF. The returned IMP for the 6-month period will be collected and retained for compliance checks. Following a physical examination, weight and checks on vital signs, the subjects will have blood samples drawn for routine haematology and biochemistry analyses.
Subjects will then undergo an endoscopy as described above. Subjects will be given new packs of IMP for the following 6 months treatment period.
24 months Visit Procedures:
Subjects will attend the clinic and the diary will be reviewed to ensure completion of the diary and to check for any changes in their condition or concomitant medication. Any changes in health and concomitant medications must be registered in the e-CRF. The returned IMP for the 6-month period will be collected and retained for compliance checks.
Following a physical examination, weight and checks on vital signs, the subjects will have blood samples drawn for routine haematology and biochemistry analyses. In addition, the subject will complete the PGI I in relation to their FAP, relative to the baseline condition.
Subjects will then undergo an endoscopy as before. In the event that a subject wishes to withdraw prior to the end of the study, they will be asked to undertake the 24 months procedures. This includes subjects who withdraw due to intolerance.

Risultati attesi (Expected results)

A total of 204 subjects will be enrolled internationally. The number of subjects per treatment group (102) is based on a coefficient of variation of 0.65, a 30% difference between the active and the placebo group, with a 90% power and a significance level of 5%. Over a 24-month period, we expect that, compared to placebo, EPA-FFA will significantly reduce the total number of polypectomies for > 5 mm polyps.

DESCRIZIONE DELLE ATTIVITÀ DELL'ASSEGNISTA

Il candidato vincitore dovrà essere in possesso di laurea in medicina e chirurgia e Specializzazione in Gastroenterologia ed aver partecipato a studi inerenti il cancro colorettale.

L'attività dell'assegnista di ricerca è legata principalmente allo svolgimento dello studio clinico ed all'analisi dei dati ottenuti. In particolare, il candidato vincitore dovrà coadiuvare il team nella selezione e l'arruolamento dei pazienti, effettuare le visite cliniche, coadiuvare il tutor nell'esecuzione degli esami endoscopici dei pazienti in studio. Inoltre il candidato vincitore dovrà coadiuvare il team nella gestione e valutazione dei video endoscopici legati allo studio. Allo scopo di adempiere ai compiti previsti dal progetto di ricerca si prevede che l'assegnista di ricerca acceda anche all'attività clinica.

Il candidato vincitore eseguirà l'arruolamento dei soggetti ed eseguirà le indagini endoscopiche previste c/o l'ambulatorio di endoscopia digestiva della UOC di Gastroenterologia Bazzoli sotto la responsabilità del Prof. Ricciardiello.

Scansione temporale attività assegnista. Primo semestre: screening candidati al trial dal database dei pazienti affetti da sindromi ereditarie ed esecuzione delle indagini endoscopiche.

Secondo Semestre: screening candidati al trial dal database dei pazienti affetti da sindromi ereditarie ed esecuzione delle indagini endoscopiche. Acquisizione e gestione dei video eseguiti durante le indagini endoscopiche. Scoring dei video.

Scheda attività assistenziale (se prevista)

ATTIVITÀ ASSISTENZIALI DELL'ASSEGNISTA/ N. ORE SETTIMANA
Frequenza dell'endoscopia digestiva ed ambulatorio prevenzione tumori digestivi presso UOC gastroenterologia Bazzoli sotto la responsabilità del Prof. Ricciardiello
18 ore settimanali
AZIENDA SANITARIA PRESSO CUI SI SVOLGERÀ L'ATTIVITÀ
Azienda Ospedaliero-Universitaria Sant'Orsola Malpighi