KEY - How to present a research article – teacher's notes

Question 1: define the type of study

A-controlled, randomized trial

B-phase 2 study

C-phase 3 study

D-open label (*a type of clinical trial in which information is not withheld from trial participants*)

E-two-stage adaptive study

- This is a phase2-3, randomized, placebo-controlled, double-blind, two-stage adaptive study
- Key words: randomized, placebo-controlled, double-blind
- It is not an open-label trial but a double-blind trial (D = false)

Question 2: describe the goal of the study

A-to determine the efficacy of propranolol over 24 weeks to reduce infantile hemangioma

B-to determine the safety of the use of propranolol in infantile hemangioma

C-to compare propranolol with standard treatment of infantile hemangioma

D-to determine the optimal duration of treatment with propranolol to reduce infantile hemangioma

E-to determine the optimal dose of propranolol to use to reduce infantile hemangioma

- The goal of the study is to investigate the use of oral paediatric propranolol for 24 weeks to reduce infantile hemangioma
- Key words: investigate, use, treatment
- It is compared to a placebo and not with standard treatment (C = false)

Question 3: defining the inclusion criteria

A-babies with a proliferating, severe infantile hemangioma

B-babies without comorbidities

C-babies with infantile hemangioma requiring systemic treatment

D-babies aged 1 to 5 months with infantile hemangioma who have never been treated

E-babies with infantile hemangioma under standard treatment

- Healthy infants with a proliferating, infantile hemangioma requiring systemic therapy (severe cases were excluded)
- Key words: infant, systemic therapy
- Severe cases were excluded (A = false); no specifications about previous treatment (D = false), no standard treatment in this disease (E = false)

Question 4: identifying the main evaluation criteria

A-successful treatment at week 24

B-successful treatment at week 24 without relapse

C-unsuccessful treatment at week 24

D-successful treatment at week 24 without any other systemic treatment

E-successful or unsuccessful treatment at week 48

- Either complete resolution of the target hemangioma or failure of trial treatment at 24 weeks
- Key words: successful treatment, resolution, failure
- Relapse after the 24 weeks visit is not part of the main evaluation criteria (B= false); the 48 weeks analysis is a secondary outcome (E=false)

Question 5: visualising the design of the study

A-in stage 1, the patients were randomized to receive either placebo or propranolol, 1mg/kg or 3mg/kg, for either 3 or 6 months

B-at the interim analysis, a dose was chosen for stage 2

C-all patients in stage 1 were randomized to receive the new dose or the placebo.

D-at the interim analysis involved the 456 patients who were randomized in stage 1

E-in stage 1, 60% of the infants in the propranolol group had successful treatment and only 4% in the placebo group

- In stage 1, patients were randomized to receive either placebo, 1mg/kg or 3mg/kg propranolol, for either 3 or 6 months. At the interim analysis, a dose was chosen for stage 2 and all patients were randomized to either placebo or the new dose
- Key words: interim analysis, stage
- The interim analysis involved the first 188 patients who had completed the week 24 visit; all the patients were not included at the same time and did not complete their treatment at the same point (D= false); the result stated in E is the conclusion of the trial, at the end of the two stages, not at the end of stage 1 – at the end of stage one the results was 63% VS 8% (E = false)

Question 6: identifying the main result of the study

A-60% of patients who were assigned to propranolol had successful treatment at week 24

B-the results vary depending on the analysis (intention-to-treat / per-protocol), probably because of premature discontinuation of treatment

C-4% of patients assigned to placebo had successful treatment at week 24

D-adverse events were significantly higher in the group assigned to propranolol then in the group assigned to placebo

E-10% of patients in whom treatment with propranolol was successful required systemic retreatment during follow-up

- 60% of patients assigned to the selected propranolol regimen and 4% of patients assigned to placebo had successful treatment at week 24
- Key words: assign, regimen, final efficacy analysis
- The results were consistent between trial stages, similar in the per protocol population (B= false)
- *Intention-to-treat analysis is a method for analyzing results in a prospective randomized study where all participants who are randomized are included in the statistical analysis and analyzed according to the group they were originally assigned, regardless of what treatment (if any) they received;*
- *Per-protocol analysis is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated. If done alone, this analysis leads to bias.*

Question 7: identifying the limitations of the study

A-a validated assessment tool was not used to assess the evolution of infantile hemangioma

B-the authors have not included a dose frequently used in clinical practice

C-the authors haven't included severe cases

D-the two groups of patients are not comparable

E-the subjective analysis of results (photographs) was not assessed with adjudication (*a standardized process for assessment of safety and efficacy of pharmacologic or device therapies in clinical trials***)**.

- The two groups are comparable (Table 1) (D = false) ; the analysis of results was assessed with adjudication (E= false)
- Key words: assessment tool, adjudication

Question 8: identifying the conclusion of the study

A-a dose of 3mg/kg/day of oral propranolol over 6 months is effective in the treatment of infantile hemangioma

B-the result of the study has a clinical relevance (*a result where a course of treatment has had genuine and quantifiable effects*)

C- the adverse events occurring in patients receiving propranolol are not an obstacle to its use

D-patients with a severe form could benefit from the efficacy of propranolol

E-a phase 4 randomized trial will be necessary in order to use it routinely

- Oral propranolol at a dose of 3mg/kg/day for 6 months is effective in the treatment of infantile hemangioma
- Key words: risk-benefit profile
- Phase 4 trials don't exist; phase 4 is about pharmacovigilance after the use of the drug in real life situations (E : false)