IRB protocol draft for "Rebound after stopping propranolol in therapy of infantile hemangioma: A Retrospective Study."

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Study Description:
1. Study Purpose and Rationale
The purpose of this study is (1) to describe, in detail, a cohort of patients with infantile hemangioma (IH) who had a good response to systemic propranolol but experienced regrowth after stopping it and (2) to identify predictors for rebound, including patient characteristics, clinical characteristics of the IH itself, and specifics of treatment with propranolol.

Summary of Relevant Background Studies
Infantile hemangioma (IH) is the most common tumor of childhood occurring in 4% to 10% of infants. The majority of IH become evident in the first few days to weeks of life.

These tumors are benign; however they undergo rapid proliferation followed by slow involution. They can compromise vital organ function, and lead to marked disfigurement. Several factors including morphology, location, and number of IH may serve as indicators of potentially problematic lesions. A recent study confirmed the significance of IH lesional morphology by dividing them into localized, segmental, and indeterminate types based upon their clinical appearance. (Chiller, 2002) A hemangioma severity scale has recently been established. (Haggstrom, 2012)

The Hemangioma Investigator Group was founded by a group of pediatric dermatologists, dedicated to advancing knowledge regarding IH and improving outcomes for affected children through excellence in collaborative research, education, and advocacy. This group has performed numerous multicenter studies relating to infantile hemangiomas and the results have been published in the medical literature.

The treatment of problematic IH has been revolutionized by the use of systemic propranolol. (Léauté-Labrèze, 2008;Maguiness, 2010) The ideal dosage has not been determined although most physicians prescribe dosages in the range of 1 to 3 mg/kg/day. In addition, the ideal length of treatment and whether tapering dose is helpful have not been clearly identified. Bagazgoitia et al have reported that 5 of their 26 patients (19%) experienced regrowth of IH after discontinuation of propranolol, especially in the deep component and before age 11 months. Early treatment withdrawal or a longer proliferative phase of IH was thought to be causes of hemangioma recurrence. (Bagazgoitia, 2011) HIG members have also experienced this phenomenon of rebound requiring reinstitution of treatment, even after the age of one year; therefore we are interested in further exploring the rebound phenomenon and its predictors. Our data will influence clinical practice by identifying a subgroup of patients that are more likely to rebound and therefore require longer treatments or dose modifications.

2. Study Design and Statistical Procedures

This study will be a multicenter retrospective chart review. We will analyze existing clinical data that was collected as part of the routine care of patients treated with propranolol for their infantile hemangiomas. A cohort of 800 subjects, from all sites will be enrolled. We hope to contribute a sample size of approximately 50 patients from CUMC.

Outcome measures are as follows:

Rebound is defined as evidence of regrowth of the hemangioma either in color and/or volume/extent.

- Predictors of rebound phenomenon (age of IH onset, sex, age of treatment initiation, duration of treatment before weaning, dose of medication etc).
- Clinical response is measured as the percent response in the size/extent/volume of hemangioma compared to baseline at the end of first treatment using the Visual Analogue Scale (VAS) described below. (McCormack, 1988) This scale has been employed in several other studies of IH. (Balma, 2012; Chakkittakandiyil, 2012; Pope, 2007) To use the VAS, the investigator is asked to mark on the scale the change in size and extent of the IH compared to the date that best results on propranolol treatment were documented. (See example of scale below, actual scale measures 100mm in length.)

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-100 0 +100

This 100 mm scale has 3 anchors: -100 (doubling in the size of the hemangioma), 0 (no change), and +100 (complete resolution). This means 5 mm corresponds to 10 % change. Practically after the investigator puts a mark on the scale, use a ruler to decide the mm distance from 0 and multiply by 2 to get the actual percentage change. (eg. + 33 mm represent 66% improvement)

Quantification of regrowth comparing the appearance of the hemangioma at its best response by evaluation of photos, as follows.

- Change in color: no change (0), mild increase (1) or moderate increase (2) and marked increase (3)
- Change in volume: no change (0), slight increase (1), moderate increase (2) and marked increase (3)
- Re-ulceration or worsening ulceration
- Evidence of functional impairment: visual, airway or others

Descriptive statistics will be calculated using means and standard deviation. For non-normally distributed data medians and IQR will be used. A chi square analysis will be perfomed to determine predictors of response. The response to treatment will be evaluated using a multiple regression analysis adjusting for repeated measures and other predictor variables such as age of start, duration of treatment, sex, medication dose, etc. The significance level will start at 5%.

3. Study Procedures

Following Institutional Review Board approval, the following procedures will take place:
- The charts of all patients treated prior to January 1, 2013 by the CUMC investigators with propranolol for their infantile hemangiomas will be preliminarily reviewed for inclusion and exclusion criteria.
- Subjects will be selected for further review according to the delineated criteria.
- Each subject will be given a unique site identifier followed by a numerical code.
- The standardized intake form will be completed for all subjects (Form 1) with routinely collected information from their medical records. Data collected includes:

1. Patient characteristics: gender, month and year of birth, age of initiating and stopping therapy, age of rebound
2. Characteristics of the hemangioma: location, subtype, size, appearance of ulceration or not
3. The maximum dosage of propranolol, the duration of treatment in months, whether dose reduction was performed before stopping, and for how long.
4. Existing digital photographs will be reviewed to monitor the appearance and extent of the hemangiomas throughout the course of treatment and following treatment cessation. All photographs have been taken following standard patient photographic consent as part of routine care. All efforts will be made to crop images so that they remain deidentifiable. However, in some cases, such as central facial or large facial hemangiomas, this may not be possible. Photos will only be reviewed by the study team at CUMC.

-CUMC study data collected will be uploaded to a secure REDCap database housed at University of California San Francisco where it will be analyzed collectively with data from other sites.

4. Study Drugs or Devices
This is not an investigative interventional trial. This is a retrospective chart review of existing data.

5. Study Instruments
Form 1-Standardized Intake Form

6. Study Subjects
All patients with infantile hemangiomas that have been treated prior to January 1, 2013 in the pediatric dermatology practices at CUMC (the investigators' practices) with propranolol and meet the following inclusion criteria will be included in this review. There will be no additional visits or studies performed for enrolled subjects. All data to be reviewed has already been collected as part of standard practices for patients with infantile hemangiomas receiving propranolol therapy.

Inclusion Criteria:
1. Patient with infantile hemangiomas treated with propranolol who discontinued therapy after at least 3 or more months.
OR
2. Patient with infantile hemangiomas treated with propranolol who have completed at least 6 months therapy.

Exclusion criteria:
1. Older than 3 years of age at treatment initiation with propanolol.
2. Insufficient patient follow-up information
3. Patient not compliant with therapy

All patients meeting the above criteria regardless of sex, background or other health status will be included in this review. We expect to enroll approximately 50 subjects from CUMC as the investigators estimate they have treated approximately 60 patients with propranolol for their infantile hemangiomas, but not all will meet the above inclusion criteria. The overall target enrollment across sites is 800 for this multicenter retrospective study. This is a convenience sample based on the number of patients estimated to meet inclusion criteria across sites.

7. Recruitment
Subjects will not be recruited for this study. Rather, all patients treated prior to January 1, 2013 by the investigators who meet the above inclusion criteria will be included in this retrospective review.

8. Informed Consent Process
We are requesting a Waiver of the usual informed consent process and HIPAA authorization as obtaining such consent and authorization would impose a greater inconvenience and violation of privacy upon subjects and families than involvement in this minimal risk study involving only analysis of existing clinical data.

9. Confidentiality of Study Data
Columbia University Medical Center, its researchers and their designees will maintain the privacy and confidentiality of all subjects' personal and health information to the extent permitted by law. Each subject will be assigned a study site and subject code number, and identifiable data will be accessible only to the primary research team, who are the same team of doctors who originally treated these patients before. All study materials and photographs will be accordingly coded. All efforts will be made to crop images so that they remain unidentifiable. However, in some circumstances, particularly central facial or large facial hemangiomas, this may not always be possible. De-identified photographs will be analyzed by CUMC study investigators only, and will not be transferred to other study sites. Other de-identified uniquely coded data will be made available to investigators at other participating sites through secure redcap database. Data will be stored securely in both electronic and paper forms that can only be accessed by the primary research team.

10. Privacy Protections
All possible efforts will be made to keep personal information confidential, but absolute confidentiality cannot be guaranteed and personal information may be disclosed if required by law. Data will be shared with participating investigators from other sites as specified below via secure REDCap database. Data sheets, (identified by a unique subject code and institution code, month of birth, year of birth and sex) will be shared

with a restricted group of investigators including: Children's Memorial Hospital at Northwestern; Cincinnati Children's Hospital; Indiana University; Children's Mercy Hospitals and Clinics at the University of Missouri; Birthmarks and Vascular Anomalies Center at University California San Francisco; Children's Hospital of Wisconsin; CHU Sainte Justine, University of Montreal; Hospital for Sick Children, University of Toronto; and the Hospital de la Santa Creu i Sant Pau Barcelona Spain. Coded data uploaded to REDCap database will be analyzed collectively. Additionally, data from this study without identifiable information may be presented at meetings and published. Organizations such as the Institutional Review Board may inspect and/or copy the research records for purposes of quality assurance and data analysis.

11. Potential Risks

No additional medical risks will be incurred as a result of this study. Access to data will be restricted as described above with emphasis on confidentiality.

12. Data and Safety Monitoring

This study is considered a minimal risk study since it involves only the systematic review of existing clinical data that was collected as part of routine care.

13. Potential Benefits

There are no direct benefits to research subjects from participating in this observational study. However, the information obtained from this study will serve as objective data as to the effectiveness of propranolol therapy for the treatment of infantile hemangiomas, benefiting future patients.

14. Alternatives

There are no proposed alternatives.

References

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