ORIGINAL REPORT

Higher Doses of Oral Propranolol for Resistant Infantile Haemangiomas

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Propranolol at 3 mg/kg/day is considered the gold standard for treating infantile haemangiomas. Nevertheless, the management of propranolol-resistant infantile haemangiomas (PRIH) remains challenging. This national multicentre retrospective observational study includes all PRIHs who received propranolol >3 mg/kg/day. The study aims to investigate the pattern of PRIHs, assess the effects and tolerance of a higher dose, and identify predictive factors for response to this increased dosage. Fifteen PRIHs were included (prevalence 0.45%), mainly females, and most presented with a large lesion. Three distinct patterns of PRIH were identified: facial segmental lesions (47%), facial localized lesions with a subcutaneous component (40%), and body-localized mixed and ulcerated lesions (13%). Six PRIH (40%) responded to the higher dose (from 3.75 to 4 mg/kg/day). Three predictive factors were significantly associated with a good response: IGIc-IH1 at the end of 3 mg/kg/day regimen (OR = 22.9, 95% CI [1.2–1844.1]), a duration of 3.5 months or more at 3 mg/kg/day (OR = 17.5, 95% CI [1.22–250.37]), and 7 months or more at >3 mg/kg/day (OR = 17.5, 95% CI [1.22–250.37]). Tolerance was generally good, although one patient experienced severe hypotension during dose escalation. Propranolol doses higher than 3 mg/kg/day may therefore be considered a potential treatment option for PRIHs.

Key words: infantile haemangioma; propranolol; resistance.

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SIGNIFICANCE

Propranolol at 3 mg/kg/day is considered the gold standard for treating infantile haemangiomas. However, a few cases of propranolol-resistant infantile haemangiomas have been reported. We therefore conducted a study to describe the characteristics of these propranolol-resistant infantile haemangiomas and evaluate the effects and tolerance of higher doses of propranolol. Our series shows that a higher dosage was effective in 40% of propranolol-resistant infantile haemangioma cases, particularly in those who showed slight improvement during the 3 mg/kg/day regimen and those with a prolonged treatment duration at 3 mg/kg/day or higher doses. Furthermore, the safety profile was deemed acceptable.

Infantile haemangioma (IH) is the most common vascular tumour of infancy (1–3). It appears at birth or within the first few weeks of life and undergoes a rapid proliferative phase, with 80% of the final size being reached by the end of the third month of life. Growth is usually complete by 9 months of age, with only 3% of IHs growing beyond this age (mainly deep and segmental IHs) (2–4). IHs then slowly involute until the average age of 4 years (4). After involution, more than half of untreated IHs present with unsightly sequelae (residual telangiectasia, fibro-fatty remnants, disfigurement) (5, 6).

Some 10–12% of all HIs (1, 7–10) are considered complicated (life or function threatening, ulceration with pain and/or lack of response to simple wound care measures, risk of permanent scarring or disfigurement), and necessitate oral propranolol. Propranolol has been shown to be effective during the proliferative phase and is well tolerated in almost all IHs at 3 mg/kg/day (after dose escalation from 1 or 2 mg/kg/day) (9). A few case reports of propranolol-resistant IH (PRIH) requiring higher doses of propranolol have been reported (11–14). However, data on the characteristics of these PRIH cases, as well as the safety and efficacy of higher doses, remain limited. We report here the first cohort of PRIH treated with higher doses of propranolol, aiming to investigate the patterns of PRIHs, assess the effects and tolerance of a higher dose, and identify predictive factors of response to this treatment regimen.

MATERIALS AND METHODS

This study was designed as a retrospective (January 2008–February 2018), national multicentre observa-

tional study. It was conducted in accordance with the principles of the Declaration of Helsinki 1975, duly revised in 2000, and was approved by the legal and ethical authorities according to the current French regulations (MR004). Data were collected from patients' medical records and clinical photographs using a standardized questionnaire.

The diagnosis of IH was based on clinical examination by paediatric dermatologists, completed if necessary by a Doppler ultrasound.

The effect of propranolol on IH's volume, colour, and ulceration was assessed using the Investigator Global Impression of Change for Infantile Hemangioma (IGIc-IH), which was developed specifically for this study to evaluate global clinical changes in IH characteristics during treatment (15). The IGIc-IH scoring criteria are as follows: –1 = worsening, 0 = stability, 1 = slight improvement, 2 = marked improvement, 3 = complete resolution.

We included all consecutive PRIHs (i.e., IHs that did not decrease in volume under the standard dose of 3 mg/kg/day of propranolol, initiated during the proliferative phase) that were subsequently treated with doses at > 3 mg/kg/day.

PRIHs were defined as having an IGIc-IH volume score ranging from –1 to 1 at the end of the 3 mg/kg/day regimen. They were then categorized as responders or non-responders to doses higher than 3 mg/kg/day: responders were those whose IGIc-IH volume score increased to a range of 2 to 3, while non-responders were those whose IGIc-IH volume score remained between –1 and 1.

Statistical analysis

To identify predictive factors for being a responder, characteristics of responders and non-responders were first compared using Fisher's exact test for qualitative data (ulceration at baseline, deep component, segmental pattern, IGIc-IH1 at the end of the 3 mg/kg/day regimen), and Mann–Whitney test for quantitative data (age at start and duration of each dosage: 1–2 mg/kg/day, 3 mg/kg/day and > 3mg/kg/day, with medians used as cut-off points). Predictors with a p-value < 0.10 were then assessed using logistic regression analysis (univariate analysis). Odds ratio (OR), corresponding 95% confidence intervals (95% CI), and p-values were calculated. Significance level α was set at $p < 0.05$. All statistical analyses were performed using MedCalc version 18.2.1 (https://www.medcalc.org/en/).

RESULTS

Nine expert centres for vascular anomalies participated in this study. Among the 3,312 IHs treated with propranolol during this 10-year-period, 15 PRIHs requiring a higher dose of propranolol were identified, corresponding to an estimated prevalence rate of 0.45%. Their characteristics are reported in **Table I**.

There were 12 females (80%) and 3 males (20%), whose PRIHs were localized on the face for 13 (87%) of them. Three distinct patterns could be distinguished (**Fig. 1**): facial segmental IHs ($n = 7$, 47%, **Fig. 2**a-L), with no associated PHACE syndrome; facial localized lesions with a subcutaneous component ($n = 6$, 40%, Fig. 2b-L); body-localized, mixed, and ulcerated lesions ($n = 2$, 13%). Overall, PRIHs were large, 13 (87%) of them measuring more than 10 cm². A total of 6 PRIHs (4 on the face, 2 on the body) were ulcerated.

None had received any other treatment before propranolol. The indication for introducing propranolol was primarily the risk of permanent scars or disfigurement ($n = 14$, 93%). Propranolol was initiated at a young age (median age of 1.8 months [0.7–13.1]), with 3 months (1–14.6) at 3 mg/kg/day. Four patients (27%) received concomitant treatments (systemic corticosteroids [$n = 3$] or topical carteolol [$n = 1$]), introduced after a median period of 4.8 months (0.1–10.8) from propranolol initiation. Adherence to propranolol was considered good. At the end of the 3 mg/kg/day regimen, the IGIc-IH score was –1, 0 (Fig. 2a-C) or 1 (Fig. 2b-C) for 4 (27%), 5 (33%) and 6 patients (40%), respectively. Ulceration healed for all 4 facial ulcerated PRIHs. Mild side effects were reported for 5 patients (33%), including sleep disturbances in 5 patients and bronchiolitis in 1 patient.

Higher doses of propranolol were started at a median age of 6.8 months (2.8–19.6), with a dose of 4 mg/kg/day for all PRIHs, except for 1, which was initially treated with 3.5 mg/kg/day, later increased to 3.75 mg/kg/day. The median duration of the higher dose regimen was 6.9 months (0.07–18.9). Concomitant treatments were discontinued for 2 patients and continued for the other 2 (systemic corticosteroids for 1, topical carteolol for 1). The median age at the end of propranolol was 14.8 months (5.2–33.1). Adherence to propranolol was considered good. Six patients (40%) experienced side effects, 5 of which were of mild severity (sleep disturbances: $n = 2$, reflux: $n = 1$ and bronchiolitis: $n = 2$). The sixth patient experienced severe symptomatic hypotension when the dose was escalated to 4 mg/kg/day, despite having no known comorbidities or concurrent medications predisposing to such an event, which led to the permanent discontinuation of propranolol.

Six PRIHs (40%) were assessed as responders, with an IGIc-IH 2 for both volume and colour (Fig. 2b-R), and 9 were non-responders: 2 (13%) who worsened, the others remained stable ($n = 3$, 20%) or slightly improved ($n = 4$, 27%) (Fig. 2a-R). The 2 ulcerated PRIHs, located on the body, still did not heal.

Using univariate analysis, 3 predictive factors for being a responder were identified individually (the other tested variables did not reach statistical significance in predicting treatment outcomes): IGIc–IH1 at the end of the

Table I. Characteristics of the 15 propranolol-resistant infantile haemangiomas treated with higher doses (> 3 mg/kg/day) of propranolol

Total no.	15
Characteristics of the 15 PRIHs	
Gender, no. (%)	
Male	3 (20)
Female	12 (80)
Birth characteristics	
Delivery at term (37–41 WA), no. (%) – 4 missing data	11 (100)
Normotrophic, no. (%) – 7 missing data	8 (100)
Past medical history, no. (%)	4 (27)
Bronchiolitis	1 (7)
Decidual haematoma	1 (7)
Gestational diabetes	1 (7)
Intrauterine growth retardation	1 (7)
PRIH pattern, no. (%)	
Face	13 (87)
Pattern 1 (segmental lesions)	7 (47)
Superficial / Mixed	3 (20) / 4 (27)
Ulcerated / non-ulcerated	3 (20) / 4 (27)
Pattern 2 (localized lesions with a subcutaneous component)	6 (40)
Mixed / Deep	3 (20) / 3 (20)
Ulcerated / non-ulcerated	1 (7) / 0 (0)
Body – Pattern 3 (localized, mixed and ulcerated lesions)	2 (13)
PRIHs size (cm^2) before propranolol introduction, no. (%)	
6–10	2 (13)
11–30	8 (54)
> 30	5 (33)
Previous systemic treatment before propranolol, no. (%)	0 (100)
Indications for propranolol, no. (%)	
Risk of permanent scars or disfigurement	14 (93)
Ulcerated IH	6 (40)
Function-threatening	4 (27)
Life-threatening IH	2 (13)
Standard regimen (3 mg/kg/day, after dose escalation from 1 or 2 mg/kg/day)	
Age at start (m), median [min–max]	1.8 [0.7–13.1]
Duration (m) at 1 to 3 mg/kg/day/ at 3 mg/kg/d, median [min–max]	3.6 [1.3–17.8] / 3 [1–14.6]
Concomitant treatments, no. (%)	4 (27)
Timeframe (m) for instauration since the beginning of P1, median [min–max]	4.8 [0.1–10.8]
Type of treatments, no. (%)	
Systemic corticoids (2 mg/kg/day)	3 (20)
Topical carteolol	1 (6.5)
Effect of propranolol (IGIc-IH scores), No. (%)	
PRIH: IGIc-IH volume -1 / IGIc-IH 0 / IGIc-IH 1	4 (27) / 5 (33) / 6 (40)
IGIc-IH colour –1 / IGIc-IH 0 / IGIc-IH 1 / IGIc-IH 2 / IGIc-IH 3	0 (0) / 6 (40) / 8 (53) / 1 (7) / 0 (0)
IGIc-IH ulceration –1 / IGIc-IH 0 / IGIc-IH 1 / IGIc-IH 2 / IGIc-IH 3	1 (16.5) / 1 (16.5) / 0 (0) / 0 (0) / 4 (67)
Side effects, no. of patients (%)	5 (33)
Sleep disturbances (mild)	4 (27)
Bronchiolitis (mild)	1 (7)
Higher doses regimen (> 3 mg/kg/day)	
Age at start (m), median [min–max]	6.8 [2.8–19.6]
Dose, *n* (%)	
4 mg/kg/day	14 (93)
3.5 to 3.75 mg/kg/day	1 (7)
Duration (m), median [min–max]	6.9 [0.07–18.9]
Concomitant treatments, no. (%)	2 (13)
Systemic corticoids (2 mg/kg/day)	1 (6.5)
Topical carteolol	1 (6.5)
Age at propranolol discontinuation (m), median [min–max]	14.8 [5.2–33.1]
Effect of propranolol (IGIc-IH scores), bo. (%)	
Responders: IGIc-IH volume 2 / IGIc-IH 3	6 (40): 6 (40) / 0 (0)
IGIc-IH colour –1 / IGIc-IH 0 / IGIc-IH 1 / IGIc-IH 2 / IGIc-IH 3	0 (0) / 0 (0) / 0 (0) / 6 (40) / 0 (0)
IGIc-IH ulceration	–*
Non-responders: IGIc-IH volume -1 / IGIc-IH 0 / IGIc-IH 1	9 (60): 2 (13) / 3 (20) / 4 (27)
IGIc-IH colour –1 / IGIc-IH 0 / IGIc-IH 1 / IGIc-IH 2 / IGIc-IH 3	0 (0) / 4 (27) / 3 (20) / 2 (13) / 0 (0)
IGIc-IH ulceration –1 / IGIc-IH 0 / IGIc-IH 1 / IGIc-IH 2 / IGIc-IH 3	0 (0) / 2 (13) / 0 (0) / 0 (0) / 0 (0)
Side effects, no. of patients (%)	6 (40)
Sleep disturbances (mild)	2 (13)
Reflux (mild)	1 (7)
Bronchiolitis (mild)	2 (13)
Symptomatic hypotension (severe, propranolol discontinuation)	1 (7)

*No responder was ulcerated at the beginning of the higher doses regimen.

IGIc-IH: Investigator Global Impression of Change for Infantile Hemangioma (-1 = worsening, 0 = stability, 1 = slight improvement, 2 = marked improvement, 3 = complete resolution); g: gram; IH: infantile haemangioma; m: month; Max: maximum; Min: minimum; no: number; PRIH: propranolol-resistant infantile haemangioma; WA: weeks of amenorrhea.

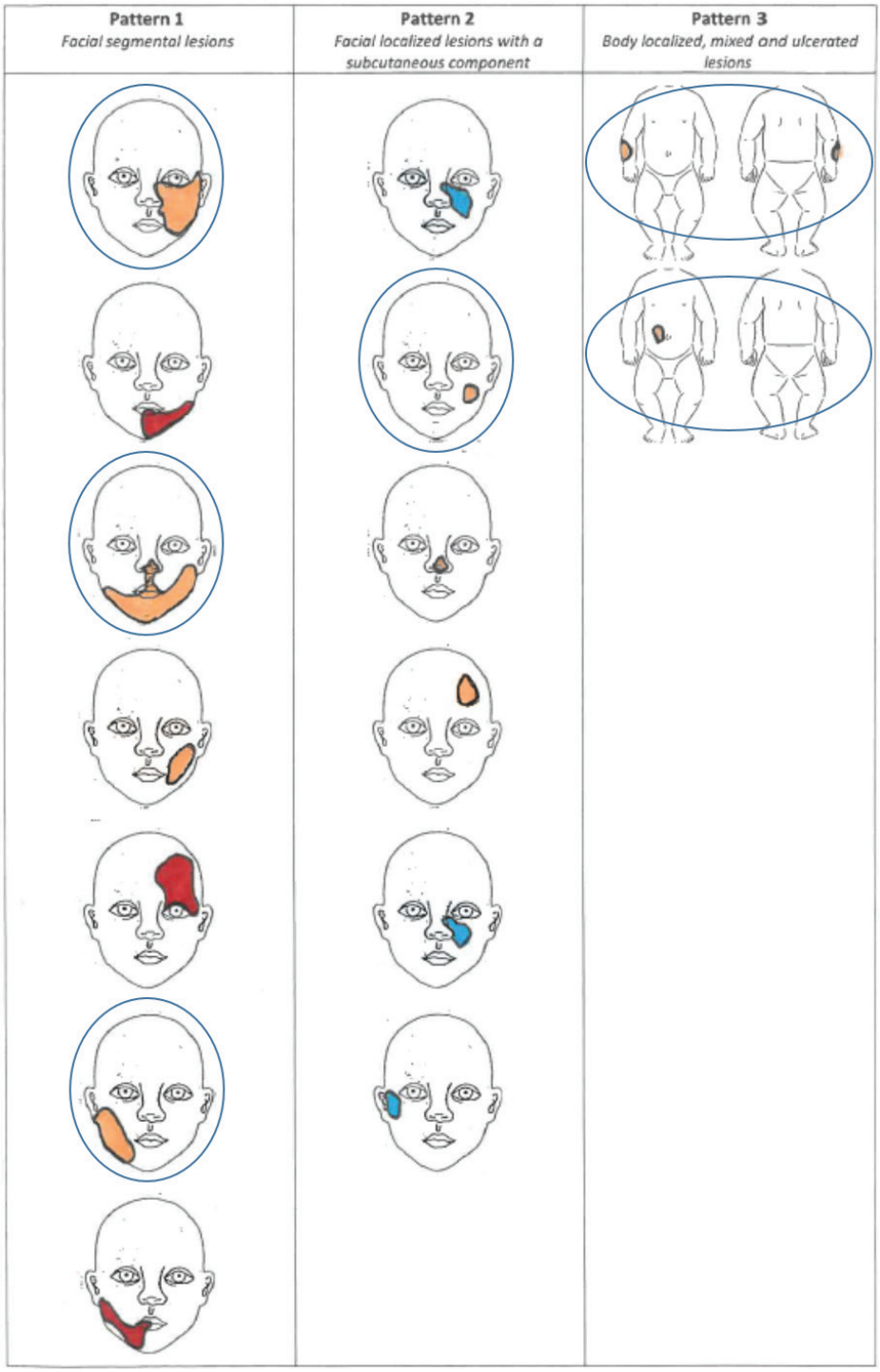

Fig. 1. Characteristics of the 15 propranolol-resistant infantile haemangiomas according to the 3 patterns. Red PRIH (propranolol-resistant infantile haemangioma): superficial lesion; orange PRIH: mixed lesion; blue PRIH: deep lesion; patient circled: ulcerated PRIH.

3 mg/kg/day regimen (OR = 22.9, 95% CI [1.2–1844.1], $p = 0.026$), a treatment duration of at least 3.5 months at 3 mg/kg/day (OR = 17.5, 95% CI [1.22–250.37], $p = 0.041$), and of at least 7 months at doses > 3mg/kg/day, ranging from 3.75 to 4 mg/kg/day (OR = 17.5, 95% CI [1.22–250.37], $p = 0.041$). Raw counts are presented in **Table II**. Due to insufficient statistical power, multivariate analysis could not be performed to determine the most significant weighted factor or to assess the relative and combined impact of the 2 treatment periods.

DISCUSSION

This is the first study to describe the clinical characteristics of PRIHs and the effects of a higher dose of

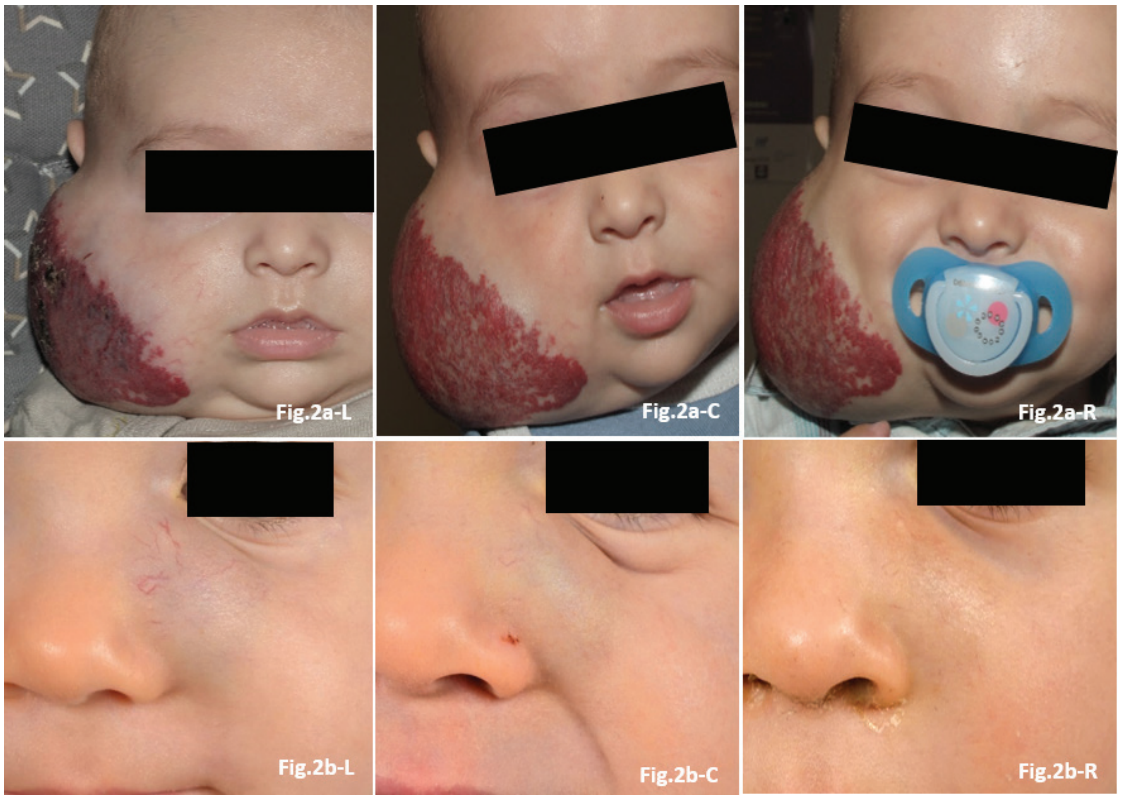

Fig. 2. Propranolol-resistant infantile haemangioma's evolution at propranolol 3 mg/kg/day and >3 mg/kg/day. (2a) Non-responder (segmental, ulcerated propranolol-resistant infantile haemangioma (PRIH): Left (2a-L): beginning of propranolol; Centre (2a-C): end of 3 mg/kg/day (IGIc-IH volume: 0, colour: 1, ulceration: 3); Right (2a-R): end of > 3 mg/kg/day (IGIc-IH volume: 1, colour: 1, ulceration: NA); (2b): Responder (deep, localized PRIH): Left (2b-L): beginning of propranolol; Centre (2b-C): end of 3 mg/kg/day (IGIc-IH volume: 1, colour: 1, ulceration: NA); Right (2b-R): end of > 3 mg/kg/day (IGIc-IH volume: 2, colour: 2, ulceration: NA).

propranolol. Our series shows that a higher propranolol dose – ranging from 3.75 to 4 mg/kg/day – was effective in 40% of PRIHs cases, particularly in those who showed a slight improvement during the 3 mg/kg/day regimen and those with a prolonged treatment duration at either 3 mg/kg/day or these higher doses. Furthermore, the safety profile was acceptable for all but 1 patient.

Our study has some limitations, including its retrospective design, with missing data and variable therapeutic regimens. The low prevalence of PRIHs, estimated at 0.45% in our study, limits statistical power but is consistent with other studies (11–14). The wide confidence intervals observed in our univariate analysis are indeed attributable to the rarity of such cases, which likewise prevented alternative statistical methods such as penalized regression or Bayesian approaches. Regarding the characteristics of PRIHs, the gender ratio and the predominant facial location were in accordance with the literature. In contrast, PRIHs more frequently presented with a deep component or a segmental pattern, compared with IHs requiring propranolol (66% vs 11%) (16–18). Three distinct patterns of PRIHs were observed in our cohort. Facial PRIHs, either segmental or localized with a subcutaneous component, have already been reported in the literature (11–14). However, to our knowledge, no body-localized mixed PRIH with persistent ulceration has been described so far. Regarding propranolol, indications and age at initiation were in accordance with the literature (4, 8–10, 16).

The mechanism behind resistance to propranolol is not yet fully understood (19). Inadequate parental compliance (20) was dismissed in our study. The spontaneous age-related involution of IHs may partially explain the limited response to higher doses which are initiated at an older age. Several hypotheses have also been proposed in the literature, including more explosive proliferation

Table II. Distribution (raw counts) of responders and non-responders according to IGIc-IH scores at the end of the 3 mg/kg/day regimen and the treatment durations at both 3 mg/kg/day and >3 mg/kg/day dosage regimens

	Responder, no.	Non-responder, no.
IGIc-IH at the end of the 3 mg/kg/day regimen, no:		
• IGIc-IH 1	8	1
• IGIc-IH –1 / IGIc-IH 0	1	5
Duration of the 3 mg/kg/day regimen, no:		
• ≥3.5 months	7	1
• <3.5 months	2	5
Duration of the >3 mg/kg/day regimen, no:		
• ≥7 months	7	1
• <7 months	2	5

IGIc-IH: Investigator Global Impression of Change for Infantile Hemangioma (–1 = worsening, 0 = stability, 1 = slight improvement), no: number.

(21) with rapid tumour growth, which may limit the diffusion of propranolol within the lesion, preventing it from reaching its therapeutic target (22). Other possibilities include a reduced number of β-receptors (20, 23), early IH differentiation into fibro-adipose tissue (24), or potentially increased first-pass hepatic metabolism, leading to reduced bioavailability of propranolol (23).

This study suggests that, with close blood pressure monitoring, increasing the dosage of propranolol at >3 mg/kg/day may be worth attempting for PRIHs, especially if a slight improvement is observed at 3 mg/kg/day. In such cases, treatment should be extended for at least 3.5 months at 3 mg/kg/day and 7 months at higher doses. One exception, however, involves persistent ulceration at 3 mg/kg/day, particularly when located on the body. In our study, these lesions did not heal even with a higher dose. While increasing the dose may enhance the anti-angiogenic effects, it also potentiates propranolol's vasoconstrictive actions, which may lead to tissue ischaemia, potentially exacerbating ulceration or inhibiting healing (25, 26). In this regard, some authors have instead suggested that a low dose of 1 mg/kg/day may promote healing (25) by improving skin perfusion and reducing ischaemia-induced ulceration. However, this remains to be demonstrated. Although clinical data supporting this approach are limited (25, 26) and no consensus currently exists, it raises important considerations for individualized dosing regimens with close follow-up in ulcerated IHs. Further prospective studies are needed to clarify the optimal dosage for this patient subset.

In cases of PRIH, other therapeutic options reported in the literature may be considered, such as systemic corticosteroids (10) or atenolol (27). More recently, oral sirolimus, an mTOR inhibitor, appears to be the most promising alternative option (19, 28–30). Treatment combinations may also be explored, although they have not been thoroughly evaluated. To date, there are no established guidelines for the treatment of choice for PRIH.

In conclusion, based on our series, propranolol at doses > 3 mg/kg/day may be considered a potential treatment option for PRIHs, except in cases of PRIH with persistent ulceration.

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IRB approval status: This study was approved by the relevant legal and ethical authorities, in accordance with current French regulations (MR004).

The authors have no conflicts of interest to declare.

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