Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: http://www.tandfonline.com/loi/ieds20

Treatment of infantile hemangiomas: therapeutic options in regard to side effects and adverse events – a review of the literature

Martine F. Raphael, Johannes M. P. J. Breur, Florine A. E. Vlasveld, Niels J. Elbert, Yves T. B. Liem, Moshe Kon, Corstiaan C. Breugem & Suzanne G. M. A. Pasmans

To cite this article: Martine F. Raphael, Johannes M. P. J. Breur, Florine A. E. Vlasveld, Niels J. Elbert, Yves T. B. Liem, Moshe Kon, Corstiaan C. Breugem & Suzanne G. M. A. Pasmans (2016) Treatment of infantile hemangiomas: therapeutic options in regard to side effects and adverse events – a review of the literature, Expert Opinion on Drug Safety, 15:2, 199-214, DOI: 10.1517/14740338.2016.1130125

To link to this article: http://dx.doi.org/10.1517/14740338.2016.1130125

Accepted author version posted online: 08 Dec 2015.
Published online: 14 Jan 2016.

EXPERT OPINION ON DRUG SAFETY, 2016
VOL. 15, NO. 2, 199–214
http://dx.doi.org/10.1517/14740338.2016.1130125

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS

Treatment of infantile hemangiomas: therapeutic options in regard to side effects and adverse events – a review of the literature

Martine F. Raphael[a*], Johannes M. P. J. Breur[b*], Florine A. E. Vlasveld[a], Niels J. Elbert[c], Yves T. B. Liem[d], Moshe Kon[e], Corstiaan C. Breugem[e*] and Suzanne G. M. A. Pasmans[a,c*]

[a]Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [b]Department of Pediatric Cardiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [c]Department of Pediatric Dermatology, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands; [d]Department of Clinical Pharmacy, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [e]Department of Pediatric Plastic Surgery, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT

Introduction: While options for treatment strategies for infantile hemangiomas (IH) are numerous, evidence-based information about agents, optimal dosage, adverse effects, treatment modality, pretreatment and treatment strategies remain limited.

Areas covered: To evaluate side effects and adverse events of medical treatment in children with infantile hemangioma, a comprehensive review of the literature was performed to provide information for daily practice. In total 254 studies were retrieved from medical databases and comprised 10,022 patients divided into 5 different treatment groups. Information about working mechanism, side effects and adverse events of therapies used as a single agent for IH are discussed and evaluated according to information from pharmacotherapeutic databases. Randomized controlled trials have only scarcely been performed for the many therapeutic options reported for IH. Short- and long-term side effects and adverse events, have not been systematically studied. Subsequently information about the medical treatment options and pharmacotheraputic databases for therapy in children with IH are incomplete.

Expert opinion: From the many therapeutic options, propranolol is the first-line approach for IH, predominantly based on clinical observation, efficacy and tolerability in the short-term. The unsolved ravels of possible short and long-term adverse events of propranolol used during early developmental stages of children need thorough review.

ARTICLE HISTORY
Received 4 September 2015
Accepted 7 December 2015
Published Online
13 January 2016

KEYWORDS
Adverse events; infantile hemangioma; side effects and therapy

1. Introduction

Infantile hemangiomas (IH) are the most frequently observed vascular tumors in infancy, found in 4–10% of Caucasian infants.[1,2] Several therapeutic regimens have been used to treat these benign tumors, with various outcomes. While options for treatment strategies for IH are numerous, evidence-based information about agents, optimal dosage, treatment modality, pretreatment and treatment strategies remains limited. In addition, side effects and adverse events from treatment of IH are rarely systematically reported.

The study of Léauté-Labrèze et al. published in 2008 demonstrated remarkable treatment results with the nonselective β-blocker propranolol on IH.[3] Consensus guidelines for pretreatment evaluation and monitoring of propranolol therapy for IH were proposed.[4] Side effects and adverse events reported in this guideline are bradycardia, hypotension, hypoglycemia, bronchospasm and hyperkalemia. In routine clinical practice, propranolol appears to be effective for IH, well tolerated and better than previous therapies at inducing regression. These observations, in conjunction with the immediate availability of the medication in pediatric formulations, resulted in the rapid and widespread adoption of propranolol for treatment of IH. This apparent success may also lead to a shift in treatment indications from initially functional only to cosmetic indications. Considering the potential overuse of β-blockers for uncomplicated IH and the uncertainty about short but especially long-term potential side effects and adverse events prompted us to review literature about what is already known.

CONTACT Martine F. Raphael m.f.raphael-2@umcutrecht.nl Department of Pediatric Dermatology and Allergology, Wilhelmina Children's Hospital, University Medical Center Utrecht G02.124, PO Box 85.500, 3508 AB Utrecht, The Netherlands.

*All participate in the Center for Congenital Vascular Anomalies Utrecht, University Medical Center Utrecht/Wilhelmina Children's Hospital, Lundlaan 6, 3584 AE, Utrecht, the Netherlands.

Article highlights

- Many therapeutic options are reported for infantile hemangioma (IH); currently, β-blocker therapy is the first-line treatment option for IH in children.
- The wide range of seemingly effective medical therapies for IH are merely lacking high level of evidence.
- Therapies utilized demonstrate numerous side effects and adverse events known for their effect during therapy, while long-term outcome and sequelae are unknown in IH patients.
- Pharmacotherapeutic databases are incomplete in information regarding the treatment options in children with IH.
- Current therapeutic strategies used in children during their early developmental growth need a thorough review of side effects and adverse events in the short- and long term.

This box summarizes key points contained in the article.

We aimed to conduct a literature review of all medical therapeutic options for IH in children to provide a more safe and optimal case-based treatment approach, as well as monitoring. We specifically studied treatment mechanism of action, side effects and adverse events. General information about side effects and adverse events of these treatment strategies from pharmacotherapeutic databases was added. Our aim was to make treatment recommendations and follow-up protocols for daily practice and subsequently highlight gaps that currently exist and that should be addressed in future clinical studies.

2. Methods

2.1. Data source and search strategy

MEDLINE, Embase and Cochrane Library were searched in April 2014 for the search terms *(treatment OR therapy) AND (hemangioma OR hemangiomas) AND (children OR infantile OR child OR juvenile OR adolescent OR neonate OR newborn OR infant)* and applied data limitation, starting from January 2008 until May 2014. The reference management program RefWorks was used for the saving and de-duplication of the articles.

2.2. Selection criteria

We included studies describing medical treatment for children aged ≤18 years with IH. The selected studies had to clearly describe whether side effects or adverse events had occurred, either with detailed symptoms or no occurrence. Studies were excluded if they focused on either surgical or laser treatment or photo- or radiotherapy. Studies not written in English, Dutch, French or German were excluded, as were reviews and meta-analyses.

2.3. Study selection

Three independent researchers (FV, NE and MR) conducted the systematic search. The selection process was performed as follows:

(1) Screen resulting articles for double publications.
(2) Screen all hits on article type and language (exclude articles meeting exclusion criteria for article type or language).
(3) Screen all abstracts on relevance (exclude articles beyond the scope of this research).
(4) Screen full text on relevance if available (include articles reporting medical treatment for children ≤18 years of age with an IH and reporting side effects and adverse events), and if full text was not available, but all necessary information (i.e. number of patients, medicine, dose, side effects and adverse events) was listed in the abstract, the particular publication was included as well.
(5) Article citation screening (add articles that met the inclusion criteria).

The researchers compared the articles remaining after this selection process, and discrepancies between reviewers were resolved by consensus.

2.4. Data extraction

Two reviewers (FV and MR) listed all included manuscripts. Number of patients, type of medication, dosage side effects and reported adverse events were registered in a database. If more than one treatment medication was used in a study, data were selected from the different treatment groups and listed as separate substudies regarding therapy and adverse effects from the included study. Available literature was evaluated for its hierarchy level of evidence (I–V).[5]

2.5. Data analysis

The pediatric hospital pharmacist (YL) analyzed reported side effects and adverse events of the medications mentioned in the included articles by using national and international pharmacotherapeutic adult databases.[6–10] The pharmacist added possible serious side effects and adverse events of used medications that were not reported in the systematic literature search.

3. Results

3.1. Search results

Initially, 1969 potential eligible studies were identified in the literature search. After excluding double reports, 1287 unique articles remained. A total of 254 studies met all inclusion criteria for this review (Figure 1 [11]). No third-party arbitration was needed for the discrepancies between reviewers.

3.2. Patients and treatment

In these 254 studies, a total of 10,022 patients were included (Table 1). All references are available as an online supplement. Six studies were case–control or retrospective comparative studies (3%), 2% were randomized controlled trials (n = 4 level I, n = 2 level II) and all other were case reports and case series from retrospective or prospective cohorts (levels III and IV).

From the included studies, subgroups of patients were made to deduct combination therapy from single-agent therapy. In total, 285 studies were revealed, with single agents in 254 studies (n = 9172 patients), covering five different treatment groups for IH (β-blockers, corticosteroids, angiotensin-converting enzyme (ACE) inhibitors, immune modulators and chemotherapy). Combination therapy was found in 31 studies (n = 850 patients). Therapies included oral, topical, intralesional and intravenous modalities. The number of patients in all studies ranged from 1 to 2013. Over 56% of all patients were treated with oral propranolol as a single agent (n = 5621). Oral prednisone was used solitary in 722 patients (7%) and topical imiquimod in 709 patients (7%). All reported side effects and adverse events were stratified per drug, therapy modality and evaluated according to adult pharmacotherapeutic databases (Tables 1 and 2). Some side effects and adverse events from therapy could not be found in these databases. Results from the former mentioned therapy groups used as a single agent (n = 254 studies) are discussed in more detail.

3.3. β-Blockers

3.3.1. Propranolol

Two randomized trials were identified that supported efficacy of propranolol, one from the search and one while performing this study.[12,13] The nonselective lipophilic β-receptor antagonist propranolol acts by inhibition of both β-1 and β-2 adrenoreceptors.[14] It is both effective during the proliferative and the involution phase of IH growth. The mechanism of action of propranolol in IH is not yet completely understood, but it is thought to originate from several effects, like vasoconstriction,[2,15] inhibition of angiogenesis,[16–23] stimulation of apoptosis [24] and inhibition of the renin–angiotensin system (RAS).[25,26] Adverse effects of oral propranolol reported in 167 studies varied from cardiovascular events, respiratory symptoms, gastrointestinal problems, metabolic alterations, skin changes and

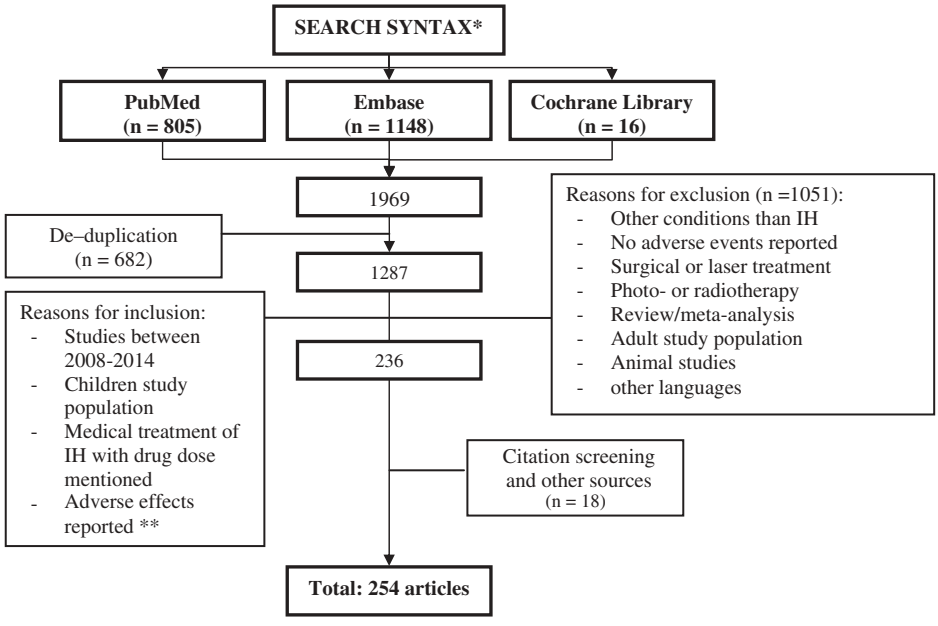

Figure 1. Flow chart according to the four-phase flow diagram of PRISMA. IH: infantile hemangioma.
*Date of search: April 2014.
**When full text was not available, but all necessary information (i.e. number of patients, medicine, dose, adverse effects) was listed in the abstract, this particular publication was included.

Table 1. Summary review study details.

Therapy	Dosage	No. of studies	No. of patients	Reported side effects and adverse events
β-Blocker				
Propranolol (oral)	0.24–4 mg/kg/day	167	5621	(Arterial)(silent) hypotension, bradycardia, respiratory symptoms (bronchiolitis, dyspnea, bronchospasm, wheezing, noisy breathing, bronchial hyperreactivity, slower rate of breathing, bronchial asthma), gastrointestinal problems, sleep disturbance, night terrors, tiredness, mood/behavioral changes, cold extremities, paleness, (silent) hypoglycemia, skin rash, exanthema or dry skin, eating problems (anorexia)[a], vomiting, nausea, diarrhea, constipation, hyperkalemia, hyperphosphatemia because of tumor lysis syndrome [a], mild right hemiparesis [a], elevated alanine transaminase/aspartate transaminase or creatine kinase-MB levels[a], abnormal electrocardiogram (not otherwise specified), prolonged sinus-arrest, hypertonia[a], dental caries[a], severe somnolence, profound mottling in lower legs, feet and hands[a], flushing of face and hands, drowsiness, vascular endothelial growth factor decrease, seizure-like episode, insomnia, agitation (irritability), delay in walking unassisted, breathholding spells, ulceration, cyanotic extremities, agranulocytosis, low body temperature, lethargy, somnolence, gastrointestinal upset, atypical events (change in neuroimaging: progressive vessel narrowing, change in neurologic status: mild hemiparesis), tissue necrosis, gastroesophageal reflux disease, no weight gain and death caused by acute renal failure after diarrhea
Propranolol (IL)	0.2 ml/cm or 1 mg/ml propranolol solution	4	35	Local pain and redness[a]
Propranolol(topical)	1% balm/ointment	5	135	None
Propranolol + steroids	*(0.5–3 mg/kg/day propranolol and 1–3 mg/kg/day prednisolone if systemically used)*	*14*	*56*	Hypoglycemia during tapering of prednisolone, bradycardia, mild hypotension, transient diarrhea, hypertension and growth retardation
Propranolol (oral) + bleomycin		*1*	*1*	
Nadolol (oral)	0.5–4 mg/kg/day	1	10	Sleep disturbance, irritability, cold extremities, gastrointestinal symptoms and fever
Acebutolol (oral)	2–10 mg/kg/day	2	7	None
Atenolol (oral)	0.5–1 mg/kg/day	5	80	Hypotension, sleep disturbance, constipation, diarrhea, cold extremities and vomiting
Brimonidine/timolol (topical)	*Brimonidine 0.2% – timolol 0.5%*	*1*	*3*	None
Timolol (topical)	0.1–0.5%, 1–5× per day	20	511	Sleep disturbance. One study reported systemic uptake: 20/24 patients (83%) had positive urine tests for timolol. Crusting and scaring
Corticosteroids				
Prednisolone (oral)	1–5 mg/kg/day or 3–5 mg/kg/day every other day	20	722	Cushingoid appearance, growth restriction, (arterial) hypertension, hirsutism, increased appetite, increased weight, fever, infection, pneumonia, severe respiratory syncytial virus, oral thrush, hypercholesterolemia, restlessness, insomnia, irritability, skin atrophy, ulceration, acne, local inflammatory reaction, hypopigmentation, glucosuria, cortisone-induced brain atrophy inducing oculomotor palsy, behavioral changes (restlessness) accompanied by increased crying, temporary adrenal insufficiency, flushing and sweating.
Triamcinolone (IL) (*in combination with betamethasone IL or dexamethasone IL*)	*0.2–1 ml/cm or 40 mg/ml solution triamcinolone (4–8 mg dexamethasone)*	*12 (7 T and 5 T/D or T/B)*	*1166 (59 combination therapy)*	Local: skin atrophy, ulceration, hypopigmentation, eyelid necrosis, hypopigmentation of the iris and ophthalmic artery occlusion Systemic: cushingoid appearance, failure to thrive, adrenal insufficiency with transient reductions of weight and linear growth, infection and hypertension
Triamcinolone (IL) + prednisolone (oral)	*Prednisolone 1–2 mg/kg every other day and triamcinolone 1–2 mg/kg*	*2*	*629*	Local: skin atrophy, ulceration, hypopigmentation and orbital cellulites Systemic: hypertension, failure to thrive and infection
Triamcinolone (IL) + propranolol (oral)		*1*	*1*	None
Betamethasone (IL)		1	36	Bruising at injection site
Angiotensin-converting enzyme-inhibitors				
Captopril (oral)	0.1–0,5. mg/kg 3 times/week	1	8	Transient mild creatinine elevation

(*Continued*)

Table 1. (Continued).

Therapy	Dosage	No. of studies	No. of patients	Reported side effects and adverse events
Immune modulators				
Imiquimod cream	5%, 3–7 times/week	10	709	Local: erythema/edema, erosions, blister, itch, peeling, crusting, ulceration, scarring, (severe) inflammatory response, desquamation and secondary infection Systemic: fever, nausea and diarrhea
Interferon-α (injection)	3,000,000 U/m^2/3 times a week	4	58	Fever, fatigue, retrosternal oppression, moderate hair loss, nausea, vomiting, flu-like symptoms, hypertriglyceridemia and elevated liver enzymes
Interferon-α (injection) + methylprednisolone (IV) + prednisolone (oral)	*0.3MU/m^2/day, 30 mg/kg/day and 2 mg/kg/day, respectively*	*1*	*1*	None
Prednisolone (oral) + interferon	*Prednisolone: 2.5–4 mg/kg/day*	*1*	*2*	No remaining neurological damage
Sirolimus	Blood levels ranged from 4.3 to 19.2 ng/ml (aimed levels range from 9 to 12 ng/ml)	1	1	Multiple times grade I/II hypertriglyceridemia, one episode of febrile neutropenia and transient episodes of mild mucositis or stomatitis
Chemotherapy				
Bleomycin (IL)	8–15 mg or 0.5 mg/kg	3	123	Local: edema, swelling, ulceration, skin rash, bruising and cellulites Systemic: nausea, loss of appetite, headache and hyperpigmentation at electrocardiograph electrodes site
Bleomycin (IL) + dexamethasone (IL)	*2–8 mg bleomycin*	*2*	*82*	No severe adverse effects such as lung fibrosis or growth restriction
Vincristine (if no response, vinblastine)	Vincristine: 0.025 mg/kg or 1.5 mg/m^2 weekly Vinblastine: 6–14 mg/m^2 weekly	2	8	Bacteremia with anemia, motor delay, peripheral neuropathy, cushingoid appearance[a] and tracheal fibrosis in child with subglottic IH[a]
Prednisolone (oral) + vincristine	*Prednisolone: 3–5 mg/kg/day* *Vincristine: 0.025 mg/kg/day weekly or 0.15–0.25 mg/kg 8 weekly*	*2*	*9*	Fever, sepsis, hypertension and central catheter infection[a]
Cyclophosphamide	4 courses of 10 mg/kg/day of cyclophosphamide and 10 mg/kg/day of MESNA for 4 consecutive days, 10 days apart	1	1	Fever with positive hemoculture[a] and pleural infusion[a]
Propranolol (oral) + vincristine + steroids		*1*	*7*	None
Total		285	10,022	

Italics: indicates double agent therapy study.
[a] Unknown adverse event according to adult pharmacotherapeutic database sources (see reference list main article).
IL: intralesional; IV: intravenous; MESNA: sodium-2-mercaptoethane sulfonate.

Table 2. Treatment side effects and adverse events according to adult pharmacotherapeutic databases.

Therapy	Side effects and adverse events	Comments
β-Blocker		
Propranolol (oral)	Regularly (1–10%): sleep disturbances, nightmares, bradycardia, cold extremities, Raynaud's phenomena, shortness of breath, tiredness and inertia. Occasionally (0.1–1%): diarrhea, nausea, vomiting. Rarely (0.01–0.1%): thrombocytopenia, heart block, deterioration heart failure, orthostatic hypotension, syncope, angioedema, hallucinations, psychosis, mood swings, confusion, amnesia, dizziness, paresthesia, visual impairment, dry eyes, deterioration claudicatio intermittens, bronchospasms, skin rash, deterioration psoriasis, alopecia. Extremely rare (≤0.01%): deterioration angina pectoris or myasthenia gravis, hyperhydrosis, positive antinuclear antibody serology, agranulocytosis, masking thyrotoxicosis, changes in fat metabolism, hypoglycemia, depression, headache, conjunctivitis, constipation, dry mouth, arthralgia, reduced renal function, impotence	
Propranolol (intralesional)		Intralesional therapy is not specified.
Propranolol (topical)		Topical therapy is not specified.
Nadolol (oral)	Bradyarrhythmia (2%), dizziness (2%), fatigue (2%), atrioventricular block (1%), cardiac dysrhythmia (1%) and heart failure (1%)[a]	
Acebutolol (oral)	Arthralgia, sleep disturbances, depression, visual hallucinations, dizziness, dry eyes, bradycardia, atrioventricular conduction prolongation, heart block, heart failure, hypotension, bronchospasms in patients with bronchial and asthmatic diseases, nausea, diarrhea, pruritus, cold extremities, fatigue and positive antinuclear antibody serology	
Atenolol (oral)	Regularly (1–10%): bradycardia, nausea, vomiting, diarrhea, tiredness and cyanotic extremities. Occasionally (0.1–1%): sleep disturbances, elevated transaminases. Rare (0.01–0.1%): thrombocytopenia, leucopenia, Raynaud's phenomena, hallucinations, psychosis, depression, confusion, dizziness, paresthesia, hypotension, aggravated heart failure, slow atrioventricular node conduction or increase in existing atrioventricular block, hepatotoxicity and bronchospasms, deterioration claudication intermittens, heart failure, headache, visual impairment, dry eyes, bronchospasms, dry mouth, hepatotoxicity, alopecia, impotence, thrombocytopenia. Extremely rare (≤0.01%): positive antinuclear antibody serology, urticaria, exanthema, angioedema, masking symptoms of hypoglycemia and thyrotoxicosis	
Timolol (topical)	Occasionally (0.1–1%): asthenia, dizziness, depression, headache, respiratory problems, nausea, dyspepsia, bradycardia and syncope. Rarely (0.01–0.1%): hypotension, palpitation, insomnia, nightmares, amnesia, deterioration myasthenia gravis, tinnitus, dry mouth, diarrhea, decompensatio cordis, Raynaud's phenomena, edema, cough, alopecia, hypoglycemia, urticaria, chest pain, skin rash, arrhythmia, heart block, cardiac arrest, positive antinuclear antibody serology, cerebral ischemia and heart failure*	*Reported side effects with the use of timolol *eye drops*
Corticosteroids		
Prednisolone (oral)	Regularly (1–10%): leukocytosis, lymphopenia, polycythemia, immunosuppression, masking infections, sodium retention, adrenal insufficiency, Cushing's syndrome, potassium excretion, increased appetite, increase in weight, diminished glucose tolerance, hypercholesterolaemia, hypertriglyceridemia, insomnia, headache, telangiectasia, petechia, bruising, muscle atrophy, muscle weakness, osteoporosis. Occasionally (0.1–1%): hypertension, atherosclerosis, thrombosis, vasculitis, ulcus pepticum, acne, changed skin pigmentation. Rarely (0.01–0.1%): allergic reactions, amenorrhea, disturbed thyroid function, depression, mood changes, psychosis, increase of intracranial pressure with papilledema, pancreatitis, aseptic bone necrosis, tachycardia, hypopotassemic alkalosis, nausea, vomiting, diarrhea, hirsutism, sepsis, heart failure, failure to thrive, convulsion, vertigo, decreased carbohydrate tolerance, hypertrophic cardiomyopathy in low birth weight children, lymphocyto- and eosinophilopenia	Frequencies are specified
Triamcinolone (intralesional)		Not specified in *intralesional* triamcinolone
Betamethasone (intralesional)		Intralesional therapy with betamethasone is not specified
Angiotensin-converting enzyme-inhibitors		
Captopril (oral)	Regularly (1–10%): dyspnea, vomiting, nausea, diarrhea, constipation, stomach ache, altered taste, dizziness, sleep disturbances, skin rash, pruritus, alopecia, weight loss, dry cough and dizziness. Occasionally (0.1–1%): tachycardia, tachyarrhythmia, angina pectoris, chest pain, palpitation, flushing, malaise, tiredness, Raynaud's phenomena, paleness, angioedema and hypotension. Rarely (0.01–0.1%): renal failure, anorexia, headache, paresthesia, stomatitis. Extremely rare (≤0.01%): neutropenia, agranulocytosis, pancytopenia, anemia, thrombocytopenia, lymphadenopathy, eosinophilia, autoimmune disorders, elevated potassium, hypoglycemia, depression, anaphylactic reactions, cardiac arrest, cerebrovascular accident, fever, myalgia, gynecosmasthia, nephrotic syndrome, liver insufficiency, pancreatitis, positive antinuclear antibody serology, urticaria, visual impairment, glossitis, confusion, ulcus pepticum, alveolitis and Stevens–Johnson syndrome	
Immune modulators		
Imiquimod cream	Frequently (≥10%): local pain and inflammation, paresthesia, pruritus and skin reaction. Regularly (1–10%): headache, infection, asthenia, lymphadenopathy, anorexia, dizziness, migraine, depression and severe local skin reaction. Increased liver enzymes, decreased number of hemoglobulin, leucocytes or thrombocytes. Occasionally (0.1–1%): flu-like symptoms, gastrointestinal complaints, anorexia, tinnitus, flushing, rhinitis, pharyngitis, arthralgia, alopecia, altered pigmentation, elevation liver enzymes, pancytopenia	

(*Continued*)

Table 2. (Continued).

Therapy	Side effects and adverse events	Comments
Interferon- α (injection)	Frequently (≥10%): hypo- and hypertension, cyanosis, diarrhea, alopecia, nausea, arrhythmia, palpitations, chest pain, flu-like symptoms, anorexia, leucopenia and hypocalcemia. Regularly (1–10%): thrombocytopenia, anemia, dry mouth, vomiting, stomachache, edema and weight loss. Occasionally (0.1–1%): electrolyte disturbance, dehydration, depression, anxiety, mental function changes, confusion, behavioral changes, amnesia, neuropathy, dizziness, paresthesia and vertigo. Rarely (0.01–0.1%): pneumonia, agranulocytosis, hemolytic anemia, autoimmune disorder, acute hypersensitivity reaction, diabetes mellitus, hyperglycemia, hyper- or hypothyroidism, suicide (attempt), coma, conjunctivitis, visual impairment, pruritus, convulsions, cardiac or respiratory arrest, myocardial infarction, congestive heart failure, pulmonary edema, dyspnea, hypertension, hypotension, proteinuria vasculitis, liver or renal failure and cerebrovascular events. Extremely rare (≤0.01%): idiopathic thrombocytopenic purpura and sarcoidosis	Side effect described with the use of interferon-–- 2a
Sirolimus (oral)	Common (≥10%): thrombocytopenia, anemia, pyrexia, hypertension, hypopotassemia, hypophosphatemia, urinary tract infection, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, abdominal pain, lymphocele, peripheral edema, arthralgia, acne, diarrhea, pain, constipation, nausea, headache, increased blood creatinine and increased blood lactate dehydrogenase. Regularly (1–10%): diabetes mellitus, bacterial/fungal and viral infections, sepsis, edema, bone necrosis, epistaxis, skin rash, skin cancer, leucopenia, neutropenia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, tachycardia, venous thrombosis, interstitial pulmonary disease, tachycardia, pleural effusion, stomatitis, ascites, abnormal liver function, proteinuria, amenorrhea, menorrhagia. Occasionally (0.1–1%): lymphoma, lymphoproliferative disease, pancytopenia, pancreatitis, nephrotic syndrome, pulmonary bleeding, pulmonary embolism, pericardial effusion. Rarely (0.01–0.1%): lymphedema, alveolar proteinosis, anaphylaxis, angioedema, dermatitis and allergic vasculitis	
Chemotherapy		
Bleomycin (intralesional)	Frequently (≥10%): damage to skin or mucous membranes (50%), fever after first injection, interstitial pneumonia (10%), which can lead to irreversible lung fibrosis and has a 1% mortality rate*. Regularly (1–10%): severe hypersensitivity reaction (1%). Occasionally (0.1–1%): minor bone marrow suppression and minor thrombocytopenia. Rarely (0.01–0.1%): hypotension, hyperpyrexia, vascular damage, such as myocardial infarction, disturbed blood flow in the brain, coronary heart disease or hemolytic uremic syndrome. Possible effects: local thrombophlebitis and vein occlusion after intravenous injection. Hyperparesthesia, anorexia and weight loss	*Pulmonary complications were not seen in patients using bleomycin for local therapy
Vincristine (intravenous)	Frequently (≥10%): neurotoxicity, such as peripheral neuropathy, decreased reflexes, paresthesia, neuralgia, muscle weakness, atactic gait and cranial nerve damage. Regularly (1–10%): constipation, transient thrombocytosis, acute dyspnea and bronchospasm and potentially life-threatening vocal cord paralysis. Occasionally (0.1–1%): severe bone marrow suppression, coronary artery disease, myocardial infarction, paralytic ileus, confusion, depression, psychosis, hallucinations, hyperuricemia and convulsions with hypertension, which can result in coma. At injection site: phlebitis, cellulites or necrosis. Rarely (0.01–0.1%): hyper- or hypotension, fever, headache, intestinal necrosis or perforation, hepatic veno-occlusive disease, inappropriate anti-diuretic hormone secretion syndrome and hypersensitivity response	
Vinblastine (intravenous)	Frequently (≥10%): leucopenia, paresthesia, peripheral neuropathy, nausea, vomiting and alopecia. Regularly (1–10%): anemia, thrombocytopenia, myelosuppression, pharyngitis, dyspnea, constipation, ileus, gastric bleeding from ulcer, hemorrhagic enterocolitis, rectal bleeding, anorexia and diarrhea. Occasionally (0.1–1%): depression, hypertension, (orthostatic) hypotension, tumor pain and general discomfort. Rarely (0.01–0.1%): inappropriate anti-diuretic hormone secretion syndrome, sensibility disturbances, peripheral neuritis, headache, convulsions, dizziness, ototoxicity, vestibular and auditive damage of the cranial nerve with deafness, disorder in balance with dizziness, nystagmus and vertigo, sinus tachycardia, angina pectoris, atrioventricular block, arrhythmia and skin blistering. Extremely rare (≤0,01%): hemolytic anemia, psychosis, erosion of eye epithelia with blepharospams, swelling of the eye lid, pre-auricular lymph nodes swelling after contact with the cornea, tinnitus, stomatitis, stomach ache, sensitive auricular lymph nodes, liver fibrosis, dermatitis, phototoxicity, muscle atrophy, urine retention, thrombotic microangiopathy with renal insufficiency, infertility, aspermia, general weakness and fever. In case of extravasation: cellulitis, necrosis, thrombophlebitis and pain at the injection site	
Cyclophosphamide (intravenous)	Frequently (≥10%): myelosuppression, alopecia, fever, (hemorrhagic) cystitis and hematuria. Regularly (1–10%): infection, mucositis, asthenia, malaise, rigor. Occasionally (0.1–1%): sepsis, neuropathy, allergic reactions, thrombocytopenia, anemia, anorexia, cardiomyopathy, myocarditis, heart failure, tachycardia and ECG changes. Rarely (0.01–0.1%): myelodysplastic syndrome, secondary malignancies, visual impairment, skin rash, chest pain, dehydration, bleeding, convulsions, (supra) ventricular arrhythmia, liver function disorders and hepatitis. Extremely rare (≤0.01%): tumor lysis syndrome, disseminated intravascular clotting, hemolytic uremic syndrome, inappropriate anti-diuretic hormone secretion syndrome, ventricular fibrillation, hypo- or hypertension, renal insufficiency, dizziness, paresthesia, conjunctivitis, ventricular/atrial fibrillation, pericarditis, hypertension, hypotension, dyspnea, stomatitis, veno-occlusive disease and multiorgan failure	

Source:[a]http://www.micromedexsolutions.com (January 2015)
http://www.cbg-meb.nl/
http://www.farmacotherapeutischkompas.nl

central nervous system (CNS) symptoms. Intralesional propranolol studies (n = 4) showed symptoms due to pain at the injection site and redness of the skin, while topical propranolol studies (n = 5) revealed no adverse effects.

3.3.2. Atenolol

Itinteang et al. suggested that propranolol acts via the RAS in regulating accelerated involution of proliferating IH by decreasing renin production in the kidneys.[25] As the kidneys predominantly express β-1 receptors, the renin–angiotensin–aldosterone system (RAAS) is most likely one of the missing links in understanding the working mechanism of both β-blockers and ACE inhibitors in the treatment of IH.[27] Atenolol is a hydrophilic β-blocker, acting on β-1 receptors with a proven efficacy in the treatment of IH.[28,29] Another explanation for the effect of atenolol could be the limited β-2-blocking potential of atenolol.[30] In the studies used in this overview, the reported side effects and adverse events noted were hypotension, sleep disturbance, constipation, diarrhea, cold extremities and vomiting.

3.3.3. Timolol

Timolol is a nonselective lipophilic β-blocker that is comparable to propranolol in mechanism of action. While timolol is available as a liquid gel, it can be topically administered to superficial IH as can propranolol cream.[31] Topical application reveals limited systemic absorption, and therefore, systemic side effects and adverse events are uncommon. However, Weibel et al. showed that 83% of children treated with topical timolol had urinary timolol excretion, suggestive of systemic uptake.[32] One study reported sleeping disturbance in one patient, which is also suggestive of systemic side effects of topical administration.[33] One randomized trial with 41 patients with superficial IH revealed effectiveness of timolol without significant differences in heart rate or blood pressure measurements compared to placebo.[34]

3.4. Corticosteroids

Although corticosteroids have been the basis of treatment in IHs for half a century, little is known about the exact working mechanism in IH. It is suggested that dexamethasone suppresses vasculogenesis of hemangioma-derived stem cells in vitro and corticosteroids diminish secretion of vascular endothelial growth factor (VEGF)-A from these stem cells in vitro.[35] A decrease in VEGF-A can sufficiently suppress vasculogenesis of hemangioma-derived stem cells in vivo. Corticosteroids are not able to suppress VEGF-A if it is from hemangioma-derived *endothelial* cells from human umbilical cords.[35] VEGF-A was detected in the proliferative phase of IH, but not in the involution phase. This might explain why corticosteroids are most effective during the proliferative phase of the IH. Corticosteroids can be used systemically, intralesional and as a topical treatment for IH. One randomized trial is known for the effectiveness of corticosteroids in IH in comparison to propranolol versus both.[36] The conclusion was that prednisolone was associated with a higher number of complications, thereby decreasing patient compliance. Propranolol showed a consistent, rapid therapeutic effect compared to prednisolone. A combination of the two had a comparable but not superior efficacy than propranolol alone. Another randomized controlled trial by Baumann et al. revealed a similar efficacy of both drugs.[37] Prednisolone showed a faster response rate while propranolol was better tolerated with significantly fewer severe short-term adverse events. In this review, side effects and adverse events of systemically used corticosteroids were seen in 20 studies with a total of 722 patients and included symptoms of metabolic, cardiovascular, endocrine, gastrointestinal, infectious, respiratory, CNS and dermatological origin. Intralesional corticosteroid therapy showed local skin symptoms varying from skin atrophy to necrosis, but it also revealed systemic side effects and adverse events (cushingoid appearance, failure to thrive, adrenal insufficiency with transient reductions of weight and linear growth, infection, hypertension).

3.5. ACE-inhibitors

The RAAS is involved in the proliferative phase of IH growth. This is supported by the observation of the negative action of propranolol on renin or the suppression of ACE by ACE-inhibitors like captopril. Both actions result in diminished production of angiotensin 2 and a subsequent regression of IH.[25] Sinaiko et al. found elevated levels of renin in children treated with ACE-inhibitors, suggesting that suppression of renin by β-blockers in addition to ACE-inhibition creates an even larger effect on IH regression.[25,38] No further evidence in literature could be found for this therapy. Adverse effects in this overview came from one study with eight patients showing a transient mild creatinine elevation in the first week of treatment in one of the patients.[27]

3.6. Immune modulators

3.6.1. Imiquimod (topical)

Imiquimod is known to influence the immune system by induction of cytokine synthesis and thereby

stimulating secretion of cytokines from macrophages, monocytes and keratinocytes in the epidermis. These cytokines, interferon (IFN), tumor necrosis factor – and interleukins (ILs) lead to a reduction of pro-angiogenic factors, cell death in endothelial cells and to a decreased tumor invasion and cell motility.[39] Furthermore, IL-12 is known for its inhibition of the angiogenesis in vivo and tube forming of endothelial cells in vitro.[40] Studies in mice revealed that imiquimod could result in a decreased activity of matrix metalloproteinase-9.[39] Therefore, the mechanism of action of imiquimod is ascribed to a cascade that results in the synthesis of cytokines that inhibit growth of IH.[41] We identified no evidence-based trials in IH. We included 10 papers with a total of 709 IH patients treated with imiquimod. Adverse effects reported were both local skin reactions and systemic symptoms of fever and gastrointestinal complaints.

3.6.2. Interferon-

INF-α is a cytokine that suppresses the growth of IH by inhibition of angiogenesis.[42] In IH, INF-α-2a and -2b are used subcutaneously. INF-α influences vessel growth by diminishing the fibroblast growth factor production or downregulation of IL-8 and the VEGF gene expression. INF-α acts on the endothelial cells directly by both impairment of proliferation and migration. Indraccolo et al. reported that INF-α reduces gene expression of endothelial cells and thereby contributing to an increase of negative regulators of angiogenesis.[43] In 58 patients using IFN-– injections for IH, several adverse effects were reported; gastrointestinal, metabolic disturbances but also general symptoms such as fever, fatigue, hair loss and flu-like symptoms.

3.6.3. Sirolimus

Mammalian target of rapamycin (mTOR) acts as a master switch for numerous cellular processes including angiogenesis and cell growth.[44] Sirolimus is an mTOR inhibitor and could therefore be beneficial in the treatment of vascular anomalies.[45] In a case report with only one patient, several side effects and adverse events occurred (hypertriglyceridemia, febrile neutropenia and mild mucositis).[46]

3.7. Chemotherapy

3.7.1. Bleomycin (intralesional)

Bleomycin is a cytotoxic agent that is able to degrade deoxyribonucleic acid (DNA), which results in an inhibition of cell replication, cell growth and DNA synthesis in tumor biology. It is used for intralesional treatment in IH. This sclerosing agent acts on vascular endothelium by induction of cell injury and disperse endothelial cells, leading to occlusion of blood vessels. Overall, it stimulates apoptosis of rapidly dividing cells, as is seen in proliferating IH.[47] The literature is limited for retrospective and prospective case studies only. In three studies of bleomycin-only intralesional therapy for IH, side effects and adverse events in 123 patients consisted of local symptoms at the injection site, but also systemic gastrointestinal complaints.

3.7.2. Vincristine

The vinca-alkaloid vincristine is known for its systemic chemotherapeutic action in malignancies. It negatively influences vascular and endothelial cell growth, inducing apoptosis and is furthermore able to stop mitosis by inhibiting the formation of microtubules.[48] Evidence-based trials with vincristine in IH are not available. Vincristine was used in two reports with eight patients of IH and reported side effects were due to infectious and peripheral nervous system origin.

3.7.3. Cyclophosphamide

Cyclophosphamide is an alkylating agent affecting DNA and the cell cycle process. It is furthermore known for its immunosuppressive effect on B and T cells.[6] One case with diffuse neonatal hemangiomatosis was treated with cyclophosphamide and suffered from fever, sepsis, catheter infection and hypertension.[49]

4. Discussion

A proper diagnosis of IH should be obtained before starting any therapy. Although this statement is beyond the scope of this report, it is especially true for initiating systemic therapy for IH with potential side effects and adverse events. This review focuses specifically on reported side effects and adverse events of any medical treatment strategy in IH. This comprehensive overview of literature was performed by stratification of all reported side effects and adverse events per drug and treatment modality instead of by frequencies in patients. The outcome demonstrates that IH are treated with a wide range of medications. In total, 10,022 patients treated in five different single-treatment medication groups for IH were included. Randomized controlled trails have only scarcely been performed for any of the reported treatment strategies. Short- and long-term side effects and adverse events are even less well studied. Pharmacotherapeutic databases are incomplete in information regarding the treatment options in children with IH.

Corticosteroids are well known for their adverse effects and are therefore no longer considered a first-

line treatment in pediatric IH. β-Blockers have become the first-line treatment modality for complicated hemangiomas. They appear to be more successful than corticosteroids, also beyond the proliferative phase,[50] while they have less side effects, although short and especially long-term adverse events are not systematically studied. The lipophilic nonselective character of propranolol causes cardiovascular, respiratory and CNS adverse effects. While the hydrophilic and more selective β-blocker atenolol is a promising alternative, its efficacy, side effects and adverse events spectrum have not been studied as extensively yet.[27–29,51–53] Topical β-blocker treatment possibly has less systemic adverse effects but it seems to be effective only in superficial IH.[31] ACE-inhibition seems to be a good alternative by its action mechanism, although literature is very limited and renal adverse effects at young age can be harmful.[27] Chemotherapy and immune modulator therapies have also been studied but are known for serious side effects and are currently replaced by less harmful strategies that appear to have at least similar effectiveness.

Tables 3 and 4 show effective therapies in children with IH, according to literature with dosage, pretreatment and treatment strategies. In addition, they depict common, unusual, serious and harmless side effects and adverse events. This overview might be helpful for the treating physician making a deliberate individualized or case-based choice for any patient with complicated IH according to current knowledge at any point during treatment. Moreover, we hope this review will be an impetus for further research since especially long-term side effects in this young patient population are unknown. While Table 3 focuses on first- and second-line therapy, Table 4 shows therapies that should only be used in case of severe complicated IH not responding to first- or second-line therapy. After consulting a vascular expert team, first-line therapy can be used in general practice, according to a standardized protocol. Second- and third-line therapy for IH though should be indicated and coordinated by a multidisciplinary team with expert knowledge on vascular abnormalities in children. Systemic immune modulator and chemotherapy medication are currently only indicated in severe complicated IH not responding to any other treatment and should exclusively be under team expert auspices. In the absence of evidence-based literature, it is hard to judge the most efficacious and safest therapy from the reviewed options.

The results of the conducted review have limitations by the low levels of evidence of included studies, small sample size for some therapy modalities, lack of available data on especially systematically studied side effects and adverse events and absence of longitudinal follow-up studies. Current review shows the side effects and adverse events listed by therapy without any denominator, which is a limitation that might leave the clinician with many uncertainties. Possibly also side effects and adverse events are underreported by this conducted review analysis. Furthermore, propranolol is offered to a much larger population than corticosteroids ever were, which is reflected in this overview and accounts for an unsolved bias. Limitations in the use of pharmacotherapeutic databases were due to lack of information about specific treatment options for IH and the fact that derived information is from treated adults mostly for other indications. Several of the observed side effects and adverse events in the pediatric IH population are not reported in adult pharmacotherapeutic databases. This shows that the available databases currently are incomplete and should be updated. This is of importance to all professionals participating in the care of IH patients.

In conclusion, there is a wide range of seemingly effective medical therapies for IH, although high level of evidence is still limited. Therapies utilized demonstrate numerous side effects and adverse events merely known for their effect during therapy, while long-term outcome and sequelae are unknown in these patients. In order to guide the clinician to judge the most efficacious and safest therapy for an individual patient, the list of therapeutic options for IH in children was reviewed. To date, first-line treatment in patients with IH is β-blocker therapy. This approach is based on clinical observation, efficacy and tolerability of propranolol, especially in the short term. Considering potential overuse of β-blockers for uncomplicated IH and the uncertainty about long-term potential side effects and adverse events still makes critically weighing the treatment indication and more comprehensive review studies of great importance.

5. Expert opinion

The first- line approach with propranolol for IH seems to be predominantly based on clinical observation, efficacy and tolerability in the short term. Only 7 years after the first report of Léauté-Labrèze et al. [3], little is known about the long-term outcome and safety. The recently performed randomized controlled trial by Léauté-Labrèze [13] showed that propranolol was effective at a dose of 3 mg/kg/day for 6 months for IH. It revealed a safety assessment by analysis of adverse events, which according to the authors included neurodevelopment revealed no notable differences

Table 3. Recommendations for first- and second-line therapy for infantile hemangioma.

Drug	Advised dosage	Pretreatment evaluation	Contraindications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side and adverse events
Source	Literature review	Dutch pediatric formulary[a] and propranolol guideline[b]	Dutch pediatric formulary		Literature review and/or pharmacotherapeutic databases[c] if >1%	Pharmacotherapeutic databases
β-Blocker						
Propranolol (oral)	2–3 mg/kg/ day	BP and HR, cardiac (family) history, ECG in children at risk	Sinus bradycardia, AV block, hypotension, respiratory disorders, heart failure, adrenal insufficiency and hypoglycemia	Clinical evaluation (i.e. history taking and physical examination)	Bradycardia, hypotension, cyanotic/cold extremities, sleep disturbance, gastrointestinal symptoms and bronchospasm, tiredness and inertia	Heart block, heart failure, hypotension, hypoglycemia, depression and agranulocytosis
Atenolol (oral)	1–2 mg/kg/ day	BP + HR, cardiac (family) history, ECG in children at risk	Sinus bradycardia, sick sinus syndrome, AV block, hypotension, respiratory disorders, heart failure, pheochromocytoma and hypoglycemia	Clinical evaluation	Bradycardia, hypotension, cyanotic extremities, sleep disturbances, tiredness and gastrointestinal symptoms	Thrombocytopenia, leucopenia, psychosis, depression, aggravated heart failure, slow AV node conduction or increase in existing AV block and hepatotoxicity
Timolol (topical)	0.1–0.5% 1–5 times a day	BP + HR, cardiac (family) history, ECG in children at risk	Asthma and other chronic pulmonary disorders, sinus bradycardia, sick-sinus syndrome, AV block heart failure, cerebrovascular insufficiency, Raynaud's phenomenon, diabetes mellitus, hypoglycemia and myasthenia gravis	Clinical evaluation for risk of systemic uptake	Sleep disturbance	Asthenia, depression, bradycardia, respiratory problems, syncope, hypotension, chest pain, arrhythmia, heart block, cardiac arrest, cerebral ischemia and heart failure
Corticosteroids						
Prednisolone (oral)	1-5 mg /kg /day, or 3–5 mg/kg/day every other day		Ulcus ventriculi or duodeni and acute infections	Clinical evaluation, growth and blood pressure	Cushing's syndrome, adrenal insufficiency, hypertension, sodium retention, potassium excretion, telangiectasia, hypercholesterolaemia, leukocytosis, lymphocytopenia, polycythemia, immunosuppression, diminished glucose tolerance, insomnia, headache, muscle weakness/atrophy, osteoporosis, failure to thrive and weight gain	Immunosuppression, sepsis, heart failure, adrenal insufficiency, muscle atrophy, osteoporosis, increase of intracranial pressure with papilledema, personality or mood changes, thromboembolism, hypertrophic cardiac myopathy in low birth weight children, pancreatitis, gastric ulcer and lymphocytopenia
Triamcinolone (intralesional)	0.2–1 ml/cm or 40 mg/ml solution triamcinolone		Hypersensitivity, ulcus ventriculi or duodeni, infections, glucocorticoid-induced myopathy, emotional unstable, psychosis, psychiatric disorders, colitis, diverticulitis, hypertension, osteoporosis and myasthenia gravis	Clinical evaluation, growth and blood pressure	*Not specified in intralesional* triamcinolone. Systemic side effects comparable with oral steroids added with local side effects: cushingoid appearance, failure to thrive and hypertension Local: skin atrophy and hypopigmentation	Eyelid necrosis, hypopigmentation of the iris, ophthalmic artery occlusion, ulceration, adrenal insufficiency and infection

[a] Kinderformularium at https://www.kinderformularium.nl
[b] Drolet et al. [4].
[c] Refs. [6]–[10].
AV: atrioventricular; BP: blood pressure; ECG: electrocardiogram; HR: heart rate.

Table 4. Recommendations in complicated infantile hemangioma not responding to first- or second-line therapy for clinicians in vascular expert teams.

Drug	Advised dosage	Pretreatment evaluation	Contraindications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side effects and adverse events
Source	Literature review	Dutch pediatric formulary[a]	Dutch pediatric formulary		Literature review and/or pharmacotherapeutic databases[b] if >1%	Pharmacotherapeutic databases
Angiotensin-converting enzyme-inhibitors						
Captopril (oral)	0.1–0.5 mg/kg three times a day	Renal function test	Renal failure or insufficiency, angioedema and caution for use in neonates	Clinical evaluation, weight, serum creatinine levels and blood count	Dyspnea, weight loss, gastrointestinal complaints, sleep disturbances, alopecia, skin rash, pruritus, dry cough and dizziness	Tachyarrhythmia, angina pectoris, chest pain, hypotension, renal failure, neutropenia, anemia, thrombocytopenia, ulcus pepticum, lymphadenopathy, autoimmune disorders, liver insufficiency and Stevens–Johnson syndrome
Immune modulators						
Imiquimod (topical)	5%, 3–7 times/week		Immunocompromised patients, autoimmune disorders and post-transplant patients	Clinical evaluation, serum blood count and liver enzymes	Local pain and inflammation, paresthesia and skin reaction, headache, infection, asthenia, dizziness, lymphadenopathy, anorexia, migraine, depression, severe local skin reaction. Increased liver enzymes, decreased hemoglobin and number of leukocytes and thrombocytes	Asthenia, lymphadenopathy, anorexia, depression, increased liver enzymes, decreased hemoglobin and number of leucocytes or thrombocytes
Interferon-α (injection)	3,000,000 U/m^2 3 times/week	Thyroid, renal and liver function tests	Severe cardiac disorder, liver of renal failure, epilepsy or central nervous disorders, history of autoimmune disorders or transplantations, unmanaged thyroid dysfunction and severe psychiatric history with depression or suicide attempt	Clinical evaluation for mood changes, blood pressure and serum electrolytes, glucose, triglycerides, thyroid and renal function, blood count and liver enzymes	Hypo- and hypertension, cyanosis, arrhythmia, palpitations, chest pain, flu-like symptoms, nausea, fatigue, anorexia, diarrhea, alopecia, leucopenia, hypocalcemia, thrombocytopenia, anemia, dry mouth, vomiting, stomachache, edema and weight loss	Hypo- and hypertension, cyanosis, arrhythmia, chest pain, leucopenia, hypocalcemia, thrombocytopenia, anemia, weight loss, electrolyte disturbance, dehydration, depression, mental function changes, behavioral changes, amnesia, neuropathy, paresthesia, pneumonia, agranulocytosis,, hemolytic anemia, autoimmune disorder, acute hypersensitivity reaction, diabetes mellitus, hyper- or hypothyroidism, suicide (attempt), coma, convulsions, cardiac or respiratory arrest, myocardial infarction, congestive heart failure, pulmonary edema, dyspnea, vasculitis, liver or renal failure, cerebrovascular effects and sarcoidosis

(*Continued*)

Table 4. (Continued).

Drug	Advised dosage	Pretreatment evaluation	Contraindications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side effects and adverse events
Sirolimus (oral)	Aimed levels range from 9 to 12 ng/ml		Hyperlipidemia, infections and post-transplant patients	Clinical evaluation for mucositis, blood pressure, and serum level of sirolimus, electrolytes, creatinine, LDH, liver function, triglycerides, blood count, urine protein excretion Add *Pneumocystis jirovecii* prophylaxis	Febrile neutropenia, infection, mucositis or stomatitis, leucopenia, thrombocytopenia, anemia, pyrexia, hypertension, electrolyte disturbances, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, abdominal pain, lymphocele, peripheral edema, arthralgia, acne, diarrhea, pain, skin rash, constipation, nausea, headache, increased blood creatinine and increased blood LDH bone necrosis, interstitial pulmonary disease, abnormal liver function, proteinuria, hemolytic uremic syndrome, venous thrombosis, tachycardia	Thrombocytopenia, anemia, hypertension, hypokalemia, urinary tract infection, pneumonitis, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, increased blood creatinine, febrile neutropenia and stomatitis
Chemotherapy						
Bleomycin (intralesional)	8–15 mg or 0.5 mg/kg		Acute lung infection, strongly decreased function or circulatory problems of the lungs and ataxia telangiectasia	Clinical evaluation	Damage to skin or mucous membranes, fever after first injection, severe hypersensitivity reaction, nausea and headache	Hypotension, hyperpyrexia, vascular damage, such as myocardial infarction, disturbed blood flow in the brain, coronary heart disease or hemolytic uremic syndrome, local thrombophlebitis and vein occlusion after intravenous injection and hyperparesthesia
Vincristine (intravenous)	0.025 mg/kg or 1.5 mg/m^2 weekly	Liver function test	Severe liver function disorders, risk of ileus, radiotherapy including the liver and hypersensitivity of vinca alkaloids	Clinical evaluation for constipation, neurological examination and serum blood count	Neurotoxicity, such as peripheral neuropathy, decreased reflexes, paresthesia, neuralgia, muscle weakness, atactic gait and cranial nerve damage, constipation, transient thrombocytosis, acute dyspnea and bronchospasm and potentially life-threatening vocal cord paralysis	Neurotoxicity, such as peripheral neuropathy, decreased reflexes, paresthesia, neuralgia, muscle weakness, atactic gait and cranial nerve damage, acute dyspnea and bronchospasm, potentially life-threatening vocal cord paralysis, severe bone marrow suppression, coronary artery disease, myocardial infarction, paralytic ileus, confusion, depression, psychosis, hyper- or hypotension, fever, intestinal necrosis or perforation, hepatic veno- occlusive disease, inappropriate ADH syndrome, hypersensitivity response, hyperuricemia and convulsions with hypertension that can result in coma. At injection site: phlebitis, cellulitis or necrosis

(*Continued*)

Table 4. (Continued).

Drug	Advised dosage	Pretreatment evaluation	Contraindications	Monitoring during treatment	Frequently reported adverse events (>1%)	Serious side effects and adverse events
Cyclophosphamide (intravenous)	4 courses of 10 mg/kg/day with MESNA for 4 consecutive days, 10 days apart	Analyze electrolyte disturbances, liver and renal function, urinating problems and exclude cystitis before initiation	Bone marrow suppression, bladder disorders, lower urinary tract obstruction or active infections, diabetes mellitus, diminished liver or kidney function, radiotherapy treatment and cardiac disorders	Clinical evaluation, serum blood count and urine erythrocytes sampling	Myelosuppression, fever, alopecia, mucositis, asthenia, malaise, rigor, (hemorrhagic) cystitis, hematuria and infection	Myelosuppression, (hemorrhagic) cystitis, hematuria, sepsis, neuropathy, cardiomyopathy, myocarditis, heart failure, tachycardia, myelodysplastic syndrome, secondary malignancies, convulsions, (supra) ventricular arrhythmia, liver function disorders, hepatitis, tumor lysis syndrome, disseminated intravascular clotting, hemolytic uremic syndrome, inappropriate ADH secretion syndrome, ventricular fibrillation, hypo- or hypertension, renal insufficiency and multiorgan failure

[a] Kinderformularium at https://www.kinderformularium.nl
[b] Refs. [6]–[10].
ADH: antidiuretic hormone; LDH: lactate dehydrogenase.

between the propranolol treatment arms and the placebo group. Unfortunately, the report does not specify in detail what variables were studied with regard to neurodevelopment and follow-up time was relatively short. The qualification of propranolol as a safe treatment strategy for IH in pediatric patients should therefore be interpreted with caution.

To date, detailed assessment of cardiovascular, gross motor and neurocognitive development has not yet been published in IH patients treated with propranolol. Subsequently, short- and long-term development outcome of treated infants with IH is unknown. Only one very recent study by Moyakine et al. showed that in 103 patients with IH treated with propanolol no evidence of psychomotor developmental delay was found.[54] It remains possible though, the authors concluded, that propranolol treatment causes subtle adverse effects, which cannot be traced with tools such as the van Wiechen scheme. And as such, they suggest that future prospective studies using universal screening tools such as the Parents Evaluation of Developmental Status, the Ages and Stages Questionnaire or more advanced neuropsychological tests are needed to support their findings. Kwon et al. reported on the analyses of infants treated with propranolol for various indications, including IH.[55] It demonstrated that no serious adverse events resulted in hospitalization and supported the perceived safety profile of propranolol. Results also implied that serious adverse events might be delayed and thus not detected during initiation of the drug treatment. It is unknown whether young infants with IH and a normotensive cardiovascular system have a different complication risk of propranolol therapy compared to those infants treated with propranolol for cardiac indications. Data on long-term outcome of patients treated with β-blockers for other indications than IH, for example, patients with arrhythmic diseases, are lacking in literature. Another concern is the observation by Gonski, who noted that 4 of 84 IH patients with oral propranolol for IH demonstrated a delay in unassisted walking.[56] In support of this, Langley summarizes many associated CNS effects of propranolol, including a meta-analysis of Lonergan, showing propranolol treatment negatively influences recall of emotional material.[57,58]We endorse the concern raised by Langley about the unknown significance of CNS effects resulting from propranolol use in IH patients during early developmental stages and/or for prolonged periods of therapy. This concern is confirmed in adult literature revealing a reduction in subsequent memory for both new and previously learned emotional material and an impairment of mood and sleep quality by propranolol.[58–60]

These findings suggest that this current therapeutic strategy needs to be updated with a thorough review of

side effects and adverse events in short and especially long term to judge β-blocker therapy in its safety. The possibility to exchange the long-term sequelae of high-dose prednisone into acceptable short-term adverse events of propranolol seemed more important than the unsolved ravels of possible long-term adverse events of propranolol. It is imperative that these unsolved ravels need thorough review during early developmental stages and especially in long-term follow-up studies to judge safety of propranolol. Moreover, in the absence of this information, we are in favor of withholding propranolol therapy for pure cosmetic indications.

Declaration of Interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as: • of interest

1. Hoornweg MJ, Smeulders MJC, Ubbink DT, et al. The prevalence and risk factors of infantile haemangiomas: a case-control study in the Dutch population. Paediatr Perinat Epidemiol. 2012;26(2):156–162.
2. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol. 2008;25(2):168–173.
3. Léauté-Labrèze C, Dumas De La Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358(24):2649–2651.
   - **The first report presenting propranolol therapy for infantile hemangiomas (IH).**
4. Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics. 2013;131(1):128–140.
   - **Reveals the consensus guideline for propanolol use in pediatric IH.**
5. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg. 2011;128(1):305–310.
6. Farmacotherapeutisch Kompas. 2015. Diemen: College voor zorgverzekeringen.
7. Summary of product characteristics (SmPCs) [Internet]. 2015. [cited 2015 Jan 27]. Available from: http://www.cbg-meb.nl
8. Informatorium Medicamentorum (Dutch manual for medicins) [Internet]. 2015. [cited 2015 Jan 27]. Available from: https://kennisbank.knmp.nl/article/informatorium_medicamentorum-_-intro.html
9. Micromedex [Internet]. 2015. [cited 2015 Jan 27]. Available from: http://www.micromedex.com
10. Aronson JK. Meyler's Side effects of drugs [Internet]. The international encyclopedia of adverse drug reactions and interactions. 15th ed. 2016. [cited 2015 Jan 27]. Available from: http://www.sciencedirect.com
11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
12. Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics. 2011;128(2):e259–e266.
   - **This randomized controlled trial is the first that showed that propanolol was effective and safe during the treatment phase.**
13. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med. 2015;372(8):735–746.
14. Westfall TC, Westfall DP. Adrenergic agonists and antagonists. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 11 ed. New York: McGraw-Hill Medical Publishing Division, New York; 2006. p. 271–295.
15. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. Br J Dermatol. 2010;163(2):269–274.
16. Chang J, Most D, Bresnick S, et al. Proliferative hemangiomas: analysis of cytokine gene expression and angiogenesis. Plast Reconstr Surg. 1999;103(1):1–9.
17. Hickey MM, Simon MC. Regulation of angiogenesis by hypoxia and hypoxia-inducible factors. Curr Top Dev Biol. 2006;76:217–257.
18. Yang EV, Sood AK, Chen M, et al. Norepinephrine upregulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. Cancer Res. 2006;66(21):10357–10364.
19. Colonna V, Resta L, Napoli A, et al. Placental hypoxia and neonatal haemangioma: clinical and histological observations. Br J Dermatol. 2010;162(1):208–209.
20. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res. 2003;92(8):827–839.
21. Kleinman ME, Greives MR, Churgin SS, et al. Hypoxia-induced mediators of stem/progenitor cell trafficking are increased in children with hemangioma. Arterioscler Thromb Vasc Biol. 2007;27(12):2664–2670.
22. Jadhav U, Chigurupati S, Lakka SS, et al. Inhibition of matrix metalloproteinase-9 reduces in vitro invasion and angiogenesis in human microvascular endothelial cells. Int J Oncol. 2004;25(5):1407–1414.
23. Takahashi K, Mulliken JB, Kozakewich HP, et al. Cellular markers that distinguish the phases of hemangioma during infancy and childhood. J Clin Invest. 1994;93(6):2357–2364.
24. Zhang D, Ma Q, Shen S, et al. Inhibition of pancreatic cancer cell proliferation by propranolol occurs through apoptosis induction: the study of beta-adrenoceptor antagonist's anticancer effect in pancreatic cancer cell. Pancreas. 2009;38(1):94–100.
25. Itinteang T, Brasch HD, Tan ST, et al. Expression of components of the renin-angiotensin system in proliferating infantile haemangioma may account for the propranolol-induced accelerated involution. J Plast Reconstr Aesthet Surg. 2011;64(6):759–765.
26. Shi R-Z, Wang J-C, Huang S-H, et al. Angiotensin II induces vascular endothelial growth factor synthesis in mesenchymal stem cells. Exp Cell Res. 2009;315(1):10–15.

27. Tan ST, Itinteang T, Day DJ, et al. Treatment of infantile haemangioma with captopril. Br J Dermatol. 2012;167 (3):619–624.
28. Raphael MF, De Graaf M, Breugem CC, et al. Atenolol: a promising alternative to propranolol for the treatment of hemangiomas. J Am Acad Dermatol. 2011;65(2):420–421.
29. De Graaf M, Raphael MF, Breugem CC, et al. Treatment of infantile haemangiomas with atenolol: comparison with a historical propranolol group. J Plast Reconstr Aesthet Surg. 2013;66(12):1732–1740.
30. Hansson L, Aberg H, Karlberg BE, et al. Controlled study of atenolol in treatment of hypertension. Br Med J. 1975;2(5967):367–370.
31. Xu G, Lv R, Zhao Z, et al. Topical propranolol for treatment of superficial infantile hemangiomas. J Am Acad Dermatol. 2012;67(6):1210–1213.
32. Weibel L, Scheer HS, Brysch M, et al. Topical betablockers for infantile hemangiomas are effective but systemically absorbed. In: Weibel L, Scheer HS, Barysch M, et al., editors. Conference: 11th congress of european society for pediatric dermatology; 2012 May 16–19;vol. 22 (1); Istanbul Turkey: ESPD; 2012. p. 1011.
33. Chakkittakandiyil A, Phillips R, Frieden IJ, et al. Timolol maleate 0.5% or 0.1% gel-forming solution for infantile hemangiomas: a retrospective, multicenter, cohort study. Pediatr Dermatol. 2012;29(1):28–31.
34. Chan H, McKay C, Adams S, et al. RCT of timolol maleate gel for superficial infantile hemangiomas in 5- to 24-week-olds. Pediatrics. 2013;131(6):e1739–e1747.
35. Greenberger S, Boscolo E, Adini I, et al. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. N Engl J Med. 2010;362(11):1005–1013.
36. Malik MA, Menon P, Rao KLN, et al. Effect of propranolol vs prednisolone vs propranolol with prednisolone in the management of infantile hemangioma: a randomized controlled study. J Pediatr Surg. 2013;48(12):2453–2459.
37. Bauman NM, McCarter RJ, Guzzetta PC, et al. Propranolol vs prednisolone for symptomatic proliferating infantile hemangiomas: a randomized clinical trial. JAMA Otolaryngol Head Neck Surg. 2014;140(4):323–330.
38. Sinaiko AR, Mirkin BL, Hendrick DA, et al. Antihypertensive effect and elimination kinetics of captopril in hypertensive children with renal disease. J Pediatr. 1983;103(5):799–805.
39. Sidbury R, Neuschler N, Neuschler E, et al. Topically applied imiquimod inhibits vascular tumor growth in vivo. J Invest Dermatol. 2003;121(5):1205–1209.
40. Duda DG, Sunamura M, Lozonschi L, et al. Direct in vitro evidence and in vivo analysis of the antiangiogenesis effects of interleukin 12. Cancer Res. 2000;60(4):1111–1116.
41. Senchak AJ, Dann M, Cable B, et al. Successful treatment of cutaneous hemangioma of infancy with topical imiquimod 5%: a report of 3 cases. Ear Nose Throat J. 2010;89(3):E21–E25.
42. Baron S, Tyring SK, Fleischmann WR, et al. The interferons. Mechanisms of action and clinical applications. JAMA. 1991;266(10):1375–1383.
43. Indraccolo S. Interferon-alpha as angiogenesis inhibitor: learning from tumor models. Autoimmunity. 2010;43 (3):244–247.
44. Vignot S, Faivre S, Aguirre D, et al. mTOR-targeted therapy of cancer with rapamycin derivatives. Ann Oncol. 2005;16(4):525–537.
45. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. Pediatr Blood Cancer. 2011;57(6):1018–1024.
46. Kaylani S, Theos AJ, Pressey JG. Treatment of infantile hemangiomas with sirolimus in a patient with PHACE syndrome. Pediatr Dermatol. 2013;30(6):e194–e197.
47. Kullendorff CM. Efficacy of bleomycin treatment for symptomatic hemangiomas in children. Pediatr Surg Int. 1997;12(7):526–528.
48. Adams DM, Wentzel MS. The role of the hematologist/oncologist in the care of patients with vascular anomalies. Pediatr Clin North Am. 2008;55(2):339–55–viii.
49. Vlahovic A, Simic R, Djokic D, et al. Diffuse neonatal hemangiomatosis treatment with cyclophosphamide: a case report. J Pediatr Hematol Oncol. 2009;31(11):858–860.
50. Zvulunov A, McCuaig C, Frieden IJ, et al. Oral propranolol therapy for infantile hemangiomas beyond the proliferation phase: a multicenter retrospective study. Pediatr Dermatol. 2011;28(2):94–98.
51. De Graaf M, Raphael MF, Breugem CC, et al. Response from the authors of "Treatment of infantile haemangiomas with atenolol: comparison with a historical propranolol group.". J Plast Reconstr Aesthet Surg. 2014;67(3):411–412.
52. Ábarzúa-Araya A, Navarrete-Dechent CP, Heusser F, et al. Atenolol versus propranolol for the treatment of infantile hemangiomas: a randomized controlled study. J Am Acad Dermatol. 2014;70(6):1045–1049.
53. Sharma VK, Fraulin FO, Dumestre DO, et al. Beta-blockers for the treatment of problematic hemangiomas. Can J Plast Surg. 2014;21(1):23–28.
54. Moyakine AV, Hermans DJ, Fuijkschot J, et al. Propranolol treatment of infantile hemangiomas does not negatively affect psychomotor development. J Am Acad Dermatol. 2015 Aug;73(2):341–342.
55. Kwon E-KM, Joachim S, Siegel DH, et al. Retrospective review of adverse effects from propranolol in infants. JAMA Dermatol. 2013;149(4):484–485.
56. Gonski K, Wargon O. Retrospective follow up of gross motor development in children using propranolol for treatment of infantile haemangioma at Sydney Children's Hospital. Australas J Dermatol. 2014;55(3):209–211.
57. Langley A, Pope E. Propranolol and central nervous system function: potential implications for paediatric patients with infantile haemangiomas. Br J Dermatol. 2015;172(1):13–23.
- **Describes the evidence for an effect of propranolol use on central nervous system function.**
58. Lonergan MH, Olivera-Figueroa LA, Pitman RK, et al. Propranolol's effects on the consolidation and reconsolidation of long-term emotional memory in healthy participants: a meta-analysis. J Psychiatry Neurosci. 2013;38(4):222–231.
59. Yamada Y, Shibuya F, Hamada J, et al. Prediction of sleep disorders induced by beta-adrenergic receptor blocking agents based on receptor occupancy. J Pharmacokinet Biopharm. 1995;23(2):131–145.
60. Stoschitzky K, Sakotnik A, Lercher P, et al. Influence of beta-blockers on melatonin release. Eur J Clin Pharmacol. 1999;55(2):111–115.