Propranolol in infantile hemangioma: Indication of major added benefit in some patients

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The Institute for Quality and Efficiency in Health Care (IQWiG) investigated in a dossier assessment whether propranolol offers an added benefit in comparison with the appropriate comparator therapy in infants with proliferating infantile haemangioma (sometimes called "strawberry mark").

According to the findings, there is an indication of major added benefit of propranolol in some children, i.e. those with haemangioma with a risk of permanent scars or disfigurement. In contrast, an added benefit is not proven for children with life- or function-threatening haemangioma, or with ulcerated haemangioma with pain or lack of response to simple wound care measures, because informative data are lacking.

Not every haemangioma requires systemic treatment

Propranolol is a beta-blocker, which is used to treat hypertension, among other things. Under the trade name Hemangiol, it has also been approved since April 2014 for the treatment of infants who have proliferating infantile haemangioma requiring treatment and who are aged five weeks to five months at the start of treatment. Infantile haemangioma occurs in an estimated three to five percent of all newborns. But only a small proportion of them require systemic treatment: when the haemangioma is life- or function-threatening, when it is ulcerated with pain or lack of response to simple wound care measures, or when it has a risk of

permanent scars or disfigurement.

The Federal Joint Committee (G-BA) specified individual treatment as appropriate comparator therapy for these therapeutic indications. The drug manufacturer further specified this comparator therapy as watchful waiting in its dossier.

Placebo arm accepted as watchful waiting

The manufacturer dossier contained data from a relevant double-blind placebo-controlled approval study (V00400SB 201), which included children aged 35 to 150 days who were at risk of permanent scars or disfigurement from their haemangioma. No conclusions on the added benefit of propranolol could be drawn for the remaining therapeutic indications.

Regular medical checks and observation of the course of disease ensured that necessary interventions could be started as soon as they were medically indicated in children in the placebo arm. Hence this study arm was accepted as watchful waiting and in the sense of individual Treatment.

Visible part of haemangioma regressed more

The main goal of the study was to assess the resolution of the target haemangioma, which was assessed in two ways. On the hand, resolution of the component of the haemangioma that was externally visible was evaluated based on the centralized assessment of photographs. On the other hand, the investigator assessed in a clinical examination (possibly also using photographs) the degree of resolution of both the visible and the deep component of the haemangioma. There was an indication of major added benefit of propranolol only for the outcome "complete or

nearly complete resolution of the visible component of the target haemangioma".

There was no proof of added benefit for some of the patient-relevant outcomes - partly because they were not investigated or no evaluable data were available, partly because there were no statistically significant differences between the treatment groups. This applied to mortality, the time to first sustained complete or nearly complete resolution of the target haemangioma, complications of the target haemangioma, health-related quality of life, serious adverse events and bronchospasm.

Positive effects predominate

Treatment discontinuations due to adverse events occurred statistically significantly more often in the placebo arm. However, these also included events resulting from worsening of the haemangioma or lack of efficacy of the study medication. Hence it could only be derived from this outcome that propranolol has no greater harm than the comparator therapy. In contrast, potential harm from propranolol could not be completely excluded regarding the outcomes "infections and infestations" and "diarrhoea".

Overall, the potential negative effects, which were mainly assessed as non-serious, did not lead to a downgrading of the positive effect in the resolution of the visible part of the target haemangioma. Hence there is an indication of major added benefit for children who are at risk of permanent scars or disfigurement and for whom watchful waiting in the sense of individual treatment is an Option.

In contrast, an added benefit of propranolol versus the appropriate comparator therapy is not proven for children with life- or function-threatening haemangioma, or with ulcerated haemangioma with pain or lack of response to simple wound care measures.

G-BA decides on the extent of added benefit

The dossier assessment is part of the overall procedure for early benefit assessments according to the Act on the Reform of the Market for Medicinal Products (AMNOG) supervised by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a commenting procedure, which may provide further information and result in a change to the benefit assessment. The G-BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

Provided by Institute for Quality and Efficiency in Health Care