IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ginkgo in Alzheimer's disease[1]

Executive Summary

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Executive summary

Research question

The aim of this research was the benefit assessment of long-term treatment with Ginkgo compounds in Alzheimer's disease compared with a) placebo, or b) a different drug or non-drug treatment option. The focus of the assessment was on patient-relevant therapy goals.

Methods

The benefit assessment considered studies in patients with mild, moderate, or severe Alzheimer's disease, including patients with mixed-type dementia (e.g., Alzheimer's disease and vascular dementia). The confirmation of diagnosis had to have been conducted according to generally accepted criteria (e.g., ICD-10, DSM-III-R, or NINCDS-ADRDA) as described in the relevant EMEA publication [1]. Studies were not considered that solely included patients with dementia due to vascular disease, Parkinson's disease, Lewy body disease, Creutzfeldt-Jacob disease, or other rare causes.

The intervention to be tested was Ginkgo biloba (hereafter referred to as "Ginkgo") in any available and approved type of administration and formulation. Placebo therapy and any other drug or non-drug interventions available and approved in Germany for Alzheimer's disease were considered as comparator interventions.

Outcomes were used that enabled an assessment of the following patient-relevant therapy goals: activities of daily living; cognitive function; health-related quality of life; other disease-related symptoms (e.g., depression, sleep-wake reversal, mania, agitation); nursing home placement (institutionalization); mortality; and treatment-related adverse events.

In addition, outcomes were used that enabled an assessment of the following therapy goals relevant to caregiving relatives (hereafter referred to as "caregivers"): quality of life of caregivers, and degree of care provided by one or several caregiver(s) or caregiving services/institution(s). As supplementary information, results were also reported that refer to the clinical disease stage according to clinical impression. Results on caregiver-relevant therapy goals and on the clinical disease stage according to clinical impression were not primarily considered in the benefit assessment. However, conclusions were to be drawn where possible regarding the association between changes in these outcomes and changes in patient-relevant outcomes.

When drugs for cognitive disorders are administered for the first time, the Drug Commission of the German Medical Profession recommends a check-up after 12 weeks in order to assess the success of therapy [2]. EMEA recommends a minimum study duration of 24 weeks for the assessment of short-term effects of antidementia drugs [1]. In order to meet both recommendations, a minimum observation period of 16 weeks was specified for this report, as

one can assume that a response to therapy can be expected within this period, and a longer term effect can be observed. No restriction of other study characteristics was planned.

A systematic literature search was conducted in 4 electronic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Studies [Clinical Studies], and CHID via ADEAR), and covered the period up to September 2007. In addition, reference lists were screened of primary publications and relevant secondary publications (such as systematic reviews, HTA reports, and comments on the question list of the Federal Joint Committee). Moreover, requests for information were sent to German manufacturers of Ginkgo compounds and to authors of publications.

The literature screening was conducted by at least 2 reviewers independently of one another. The prespecified methodological procedures (report plan) and IQWiG's preliminary benefit assessment (preliminary report) were published on the Internet and interested parties were invited to submit written comments. If changes were made on the basis of unclear aspects presented in the comments, this was noted in the final report. Relevant unclear aspects concerning the written comments on the preliminary report were discussed in 2 scientific debates, and the final report was subsequently produced.

Results

The electronic literature search in the relevant bibliographic databases, the screening of reference lists of secondary publications, as well as contact with manufacturers and authors enabled the identification of 7 completed and largely published studies fulfilling the inclusion criteria defined for this report.

All studies included used the standardized Ginkgo extract EGb 761 produced by the German manufacturer Dr Willmar Schwabe Arzneimittel & Co. KG (Karlsruhe, Germany). Except for the DIGGER 2007 study, all studies were also sponsored by this manufacturer.

Six of the studies included (DIGGER 2007, Kanowski 1996, Le Bars 1997, Napryeyenko 2007, Schneider 2005, and Schwabe 2008) compared Ginkgo with placebo. Yancheva 2006 investigated Ginkgo versus active comparators (donepezil as well as a combination therapy with Ginkgo and donepezil). The study and publication quality of Schneider 2005 did not show any evident deficiencies; DIGGER 2007, Kanowski 1996, Le Bars 1997, Napryeyenko 2007, Schwabe 2008, and Yancheva 2006 showed minor deficiencies.

Overall, high heterogeneity was shown for most outcomes between the studies considered. The factors "age", "dose", and "accompanying psychopathological symptoms" were identified as possible effect modifiers. However, only limited subgroup analyses were possible for the factors "age" and "accompanying psychopathological symptoms", as the relevant information was not available for all studies. Results were summarized separately for the 120 mg and 240 mg doses if substantial heterogeneity was evident. This was the case for most outcomes. The results of patients treated with high-dose Ginkgo were, at least from a

qualitative point of view, largely homogeneous and are therefore of higher relevance for the benefit assessment. If not otherwise noted, the conclusion is based on the high-dose data.

For the therapy goal “activities of daily living”, a benefit of Ginkgo was demonstrated when only studies were considered in which a dose of 240 mg daily was used. For the therapy goal “accompanying psychopathological symptoms”, there was an indication of a benefit of Ginkgo only with regard to general psychopathology. There was no clear indication of, but merely a tendency towards a positive effect of Ginkgo on depressive symptoms. For the therapy goal “cognition”, the studies provided an indication of a benefit of Ginkgo. With regard to health-related quality of life, a statement on the benefit of high-dose Ginkgo can only be made on the basis of the study by Schwabe 2008; even though a statistically significant advantage for Ginkgo was shown, only an indication of a benefit of Ginkgo with regard to this outcome was confirmed due to the scarcity of the data available. No study data were available regarding the assessment of nursing home placement (institutionalization). Overall, only few deaths were reported in the studies. For this reason, no indication of a beneficial or detrimental effect of Ginkgo on mortality can be inferred. The results on adverse drug effects were in general inconsistent. Regarding serious adverse events and overall adverse events, there was no indication of harm caused by Ginkgo. However, there was evidence that more patients discontinued the study due to adverse events with Ginkgo than with placebo.

Data on the quality of life of caregivers were only found in one study on low-dose Ginkgo, so that no statement can be made on the effects of high-dose Ginkgo. Data on the emotional stress of caregivers were found in 2 studies on high-dose Ginkgo. There was an indication of a benefit of Ginkgo; however, no statement on the effect size can be made due to the high heterogeneity of results. Only data from one study on low-dose Ginkgo were available for the assessment of the degree of care; a statement on the effects of high-dose Ginkgo is therefore not possible. Regarding the global clinical impression, the results of studies on high-dose Ginkgo were in favour of Ginkgo; there is hence evidence of a beneficial effect, even though the effect size varied considerably between studies.

Even though the factors “age” and “accompanying psychopathology” showed a modifying effect primarily on the outcomes “activities of daily living” and “cognitive function”, it is difficult to interpret the data due to insufficient information. As the studies were very heterogeneous regarding various factors, it is not possible to make a clear distinction between individual modifying factors. However, it can be noted that the average age of patients and the extent of the accompanying psychopathology are potentially relevant factors that may at least in part explain heterogeneity.

Conclusion

For the therapy goal “activities of daily living”, there is evidence of a benefit of high-dose (240 mg daily) Ginkgo extract EGb 761. In patients taking this dose, there are also indications of a benefit for the therapy goals “cognitive function” and “general psychopathological symptoms”, as well as for the caregiver-relevant therapy goal “quality of life of caregivers”

(measured on the basis of caregivers' emotional stress). However, the conclusion that Ginkgo has a beneficial effect is based on very heterogeneous results; therefore no summarizing conclusion can be made on the potential effect size. In addition, there is an indication that this benefit is only present in patients with accompanying psychopathological symptoms. Moreover, it needs to be considered that the results were strongly affected by 2 studies conducted in an Eastern European health-care setting with specific patient populations (among other things, patients with a high rate of accompanying psychopathological symptoms).

Overall, the results on adverse drug effects were inconsistent. With regard to serious adverse events and overall adverse events, there was no indication of harm caused by Ginkgo. However, evidence was available that with Ginkgo, more patients discontinued the study due to adverse events than with placebo.

Due to the high heterogeneity between studies, no conclusive statement can be made on the benefit of low-dose Ginkgo (120 mg daily). Relevant data on Ginkgo extracts other than Ginkgo extract EGb 761 were not available.

The benefit of Ginkgo compared with other drugs approved for Alzheimer's disease (such as cholinesterase inhibitors or memantine) is unclear, as only one explorative study investigated a direct comparison (vs. donepezil)

Despite the consideration of the Ginkgo dose in the interpretation of results, the considerable heterogeneity could not be adequately explained. An assessment of the effect size was not possible on the basis of the available study data. Additional studies designed specifically to investigate individual subgroups of patients with Alzheimer's disease are needed to enable subgroup-specific conclusions to be drawn. As the results of this benefit assessment were dominated by 2 studies that were not conducted in the health-care setting of a Western country, future studies should be carried out in such a setting. If, due to available treatment options (e.g., cholinesterase inhibitors), placebo-controlled studies seem difficult to conduct, appropriate comparator studies with other antidementia drugs could be an alternative option. Data from long-term studies would also be desirable to assess potential beneficial and adverse effects of long-term therapy with Ginkgo.

Keywords: Ginkgo compounds, Ginkgo biloba, EGb 761, antidementia drugs, Alzheimer's disease, systematic review

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