IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Working Papers

Memantine in Alzheimer's disease: Results of the unpublished studies IE2101 and MEM-MD-22 as well as unpublished responder analyses[1]

[1] Translation of the executive summary of the working paper "Memantin bei Alzheimer Demenz: Ergebnisse der unpublizierten Studien IE2101 und MEM-MD-22 sowie unpublizierter Responderanalysen" (Version 1.0; Status: 01.07.2010). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Memantine in Alzheimer's disease: Results of the unpublished studies IE2101 and MEM-MD-22 as well as unpublished responder analyses

Executive summary

Background

In July 2009 the Institute for Quality and Efficiency in Health Care (IQWiG) prepared a final report on the topic "Memantine in Alzheimer's disease" (Commission A05-19C). At the time of the assessment, the results of the relevant studies IE2101 and MEM-MD-22 could not be considered. This was due to the fact that these 2 studies had not been fully published and that the manufacturer Merz, despite several requests, did not provide the corresponding clinical study reports (CSRs). In the first quarter of 2010, Merz finally submitted the CSRs of studies IE2101 and MEM-MD-22 to the Federal Joint Committee (G-BA). In addition, Merz also presented responder analyses that had been calculated post-hoc and had previously been unpublished.

Research question

The aim of this working paper is to answer the following research questions:

1. What impact do the results of the studies IE2101 and MEM-MD-22 have on the conclusions of the final report A05-19C ("Memantine in Alzheimer's disease")?

2. What impact do the post-hoc responder analyses calculated by Merz have on the conclusions of the final report A05-19C ("Memantine in Alzheimer's disease")?

Methods

For the present working paper, the documents submitted by Merz to the G-BA were considered. These referred to the CSR of study IE2101, the CSR of study MEM-MD-22, as well as to a letter from Merz to the G-BA of 4 March 2010 concerning the responder analyses. In addition, information already available for the final report A05-19C was considered. An additional literature search was not conducted.

The tables of the final report A05-19C were supplemented with the additional information on the unpublished studies IE2101 and MEM-MD-22. If meaningful and feasible, new meta-analyses were subsequently calculated considering the results of the 2 studies IE2101 and MEM-MD-22. It was then assessed whether the new results change the conclusions of final report A05-19C.

An overall evaluation was made of the letter from Merz of 4 March 2010, including the enclosed responder analyses. In this context, it was described whether the information presented change the conclusions of final report A05-19C.

Each of the working steps described above was conducted on the basis of the methods outlined in final report A05-19C.

Results

Assessment of the studies IE2101 and MEM-MD-22

Both studies IE2101 and MEM-MD-22 were double-blind, placebo-controlled trials investigating the monotherapy of memantine in patients with moderate to severe Alzheimer's disease. The studies were performed in Japan and the United States respectively. Both lasted 24 weeks, and included 208 and 265 patients respectively. They were therefore similar in duration and size to the other relevant studies (or to the study subgroups relevant to the assessment).

Compared to the other studies, no specific inclusion or exclusion criteria applied to study IE2101. In contrast, MEM-MD-22 was the only study that explicitly included only patients living in a nursing home. (However, as in the other studies, they had to be in a stable clinical condition.) In addition, patients had to be at least 65 years old (in the other studies: at least 50 years old).

Both studies IE2101 and MEM-MD-22 showed no major deficits in study quality.

Taking both new studies into account, the results for relevant outcomes compared to those of final report A05-19C were as follows:

- Regarding activities of daily living, an almost unchanged total effect was shown. Working paper: 0.13 standard deviations (SD), (95% CI [0.04; 0.21], p = 0.003); A05-19C: 0.14 SD (95% CI [0.05; 0.23], p = 0.002).

- Regarding cognitive function, an almost unchanged total effect was shown. Working paper: 0.21 SD (95% CI [0.09; 0.32], p < 0.001); A05-19C: 0.20 SD (95% CI [0.07; 0.33], p = 0.002).

- Regarding concomitant psychopathological symptoms, only a slightly changed total effect was shown, which did not affect the overall conclusion. Working paper: 0.87 scale points (95% CI [-0.26; 2.00], p = 0.132); A05-19C: 1.10 scale points (95% CI [-0.23; 2.43], p = 0.106).

- Regarding the number of deaths, an almost unchanged overall estimate was shown, with a slightly increased precision that did not affect the overall conclusion. Working paper: relative risk (RR) 0.85 (95% CI [0.48; 1.51], p = 0.580); A05-19C: RR 0.88 (95% CI [0.42; 1.83], p = 0.727).

- Regarding serious adverse events, a slightly changed total effect was shown, without affecting the overall conclusion. Working paper: RR 0.87 (95 % CI [0.71; 1.08], p = 0.218); A05-19C: RR 0.97 (95 % CI [0.75; 1.24], p = 0.787).

- Regarding study discontinuations due to adverse events, a slightly changed total effect was shown, without affecting the overall conclusion. Working paper: RR 0.79 (95% CI [0.61; 1.03], p = 0.085); A05-19C: RR 0.84 (95% CI [0.59; 1.19], p = 0.322).

- Regarding the overall rate of adverse events, a slightly changed total effect was shown, without affecting the overall conclusion. Working paper: RR 0.98 (95% CI [0.94; 1.02], p = 0.264); A05-19C: RR 1.00 (95% CI [0.95; 1.06], p = 0.863)

- Regarding the global clinical impression, a practically unchanged total effect was shown. Working paper: 0.16 SD (95% CI [0.06; 0.26], p = 0.002); A05-19C: 0.18 SD (95% CI [0.05; 0.30], p = 0.005).

No case resulted in a change of the conclusions in the final report A05-19C.

Relevant subgroup analyses were only available in study IE2101 for the outcomes activities of daily living, cognitive function, and global clinical impression. The findings had no impact on the conclusions of final report A05-19C.

Assessment of responder analyses

The letter from Merz of 4 March 2010 included on the one hand references to responder analyses of the European regulatory authority, the European Medicines Agency (EMA, formerly EMEA), while on the other, analyses calculated by Merz were presented.

No proof of benefit of memantine could be inferred from the responders analyses presented in EMA's European Public Assessment Report (EPAR) for the following reasons: the analyses included were combined analyses considering the global clinical impression; the response criteria for activities of daily living were not clearly named; and overall the data were not presented with sufficient transparency and in part contradicted other analyses (evaluation of cholinesterase inhibitors). In addition, from a current point of view the analyses were no longer up to date.

The newly calculated responder analyses also fail to prove the benefit of memantine: they referred to a selective choice of studies (6 out of 9 relevant studies); they also considered patients not treated according to approval status; the summarizing analysis was performed without presenting the results of the individual studies; the response criterion for activities of daily living remained unclear; and the data themselves were contradictory. However, it seems possible that a benefit of memantine in the area of cognitive function might be shown if analyses were conducted and reported adequately. This remains completely unclear for the area of activities of daily living; analyses with an appropriate response criterion are generally lacking here. In addition, both for cognitive function and for activities of daily living, further sensitivity analyses are required in which patients for whom no end-of-study measurements were available are evaluated as non-responders (in the sense of a relevant clinical deterioration).

Conclusions

A proof of benefit of memantine can neither be inferred from the unpublished studies IE2101 and MEM-MD-22 nor from the responder analyses newly calculated by Merz.

However, it seems possible that if analyses were conducted and reported adequately, such a benefit might be shown in the area of cognitive function. This remains completely unclear for the area of activities of daily living; analyses with an appropriate response criterion are generally required here.

On the basis of the information currently available, no changes arise in the conclusions of final report A05-19C.

Keywords: memantine, Alzheimer's disease, unpublished data

The full working paper (German version) is available under www.iqwig.de