Pharmacoepidemiologic Cohort Study on the Administration of Remifemin® / Remifemin® plus in Patients with Breast Cancer, Including Hormone Receptor-Positive Tumors

Henneicke-von Zepelin[1], H. -H., Becher, H.[2], Schröder-Bernhardi, D.[3], Stammwitz, U.[1]
[1] Schaper & Brümmer GmbH & Co. KG, Salzgitter, Germany
[2] Ruprecht-Karls-Universität , Heidelberg, Germany
[3] IMS HEALTH GmbH & Co. OHG, Frankfurt/Main, Germany

please address correspondence to: h.v.zepelin@schaper-bruemmer.de

A large number of breast cancer patients simultaneously suffers from climacteric complaints due to hormone deficiencies. Primary and adjuvant tumor therapies can even worsen these complaints – in particular vasomotor symptoms. Even postmenopausal patients without acute climacteric symptomatology can suffer from recurring complaints [1]. Hormone replacement therapy is not safe for estrogen receptor-positive tumors [2, 3]. Since experimental and clinical studies did not reveal any estrogenic effects for the two gynecologic herbal preparations Remifemin® and Remifemin® plus, which contain an isopropanolic Cimicifuga extract, they are not contra-indicated in patients who had estrogen-dependent tumors [4-7]. The system for spontaneous reports of adverse drug events also does not indicate any promotion of recurrences in breast cancer patients. The subject investigation contributes further human data.

The study population of this comparative database-based cohort study with a moved back baseline consisted of breast cancer patients (including those with hormone receptor-positive tumors) in the anamnesis who had been treated between 1992 and 2003 in medical offices connected to the IMS® 'Disease Analyzer' - mediplus® - database [8]. Data from 1,151 medical clinics were analyzed (1,278 patients of general physicians, practitioners, and internists and 233 gynecologists). The total number of breast cancer patients was 47,795 including suspected diagnosis. Cases with primarily metastasizing tumor, unconfirmed suspected diagnosis, other primary tumors prior to breast cancer, administration of other Cimicifuga preparations or an observation period of less than 6 months were excluded from the analysis. The target criterion was the tumor-free survival time after the breast cancer diagnosis. Recurrences were recorded in the database by means of ICD-codes, specific therapeutic measures or free text entries. The primary influence variable was the treatment with Remifemin® / Remifemin® plus after diagnosis and/or primary therapy of a breast cancer. This was a non-inferiority study. A significance level of 0.05 and an equivalence range of +/- 25 % was used. With a hazard ratio as target parameter, this corresponds to a range of 0.8 to 1.25 (H_0: RR > 1.25). The statistical evaluation occurred with Kaplan-Meier-estimates and by means of a survival time analysis in the Proportional Hazards model. As relevant co-variables, the following was considered: age at diagnosis, Tamoxifen-therapy, number of the database-entries per annum, year of diagnosis, application of further natural treatments.

18,861 breast cancer patients were included in the analysis. Of these, 1,102 patients were assigned to the Remifemin® / Remifemin® plus-group and 17,759 to the control group. The mean age at diagnosis was 61.4 years. The mean observation period between diagnosis and last database entry was 3.6 years, for Remifemin®/Remifemin® plus-users on average 4.6 years. On the whole, there was a high data consistency. There were no indications of a lacking validity or representativity of the 'Disease Analyzer' database regarding the questions to be analyzed. The hypothesis of a relevant increase of the risk of recurrences under / after Remifemin® / Remifemin® plus treatment in comparison with women not treated with these preparations can be rejected.

Overall and in all age classes, the direct group comparison rather showed lower rates of recurrences in Remifemin® / Remifemin® plus-patients. While 14 % of the women in the control group had developed a recurrence already two years after first diagnosis, this rate of recurrences was reached in the Remifemin® / Remifemin® plus-group only after 6.5 years (fig. 1).
The effect on the rate of recurrences, indicated as Hazard Rate Ratio, was 0.83 (95 % confidence interval 0.69 - 0.99).
In comparison to the control group, there was a 17 % smaller risk for a recurrence under Remifemin® / Remifemin® plus. This effect was consistent in all subgroup analyses. This analysis therefore also supports the drug safety of of Remifemin® / Remifemin® plus in breast cancer patients. By using the mediplus® - database, previously unavailable case numbers and post observation periods could be implemented.

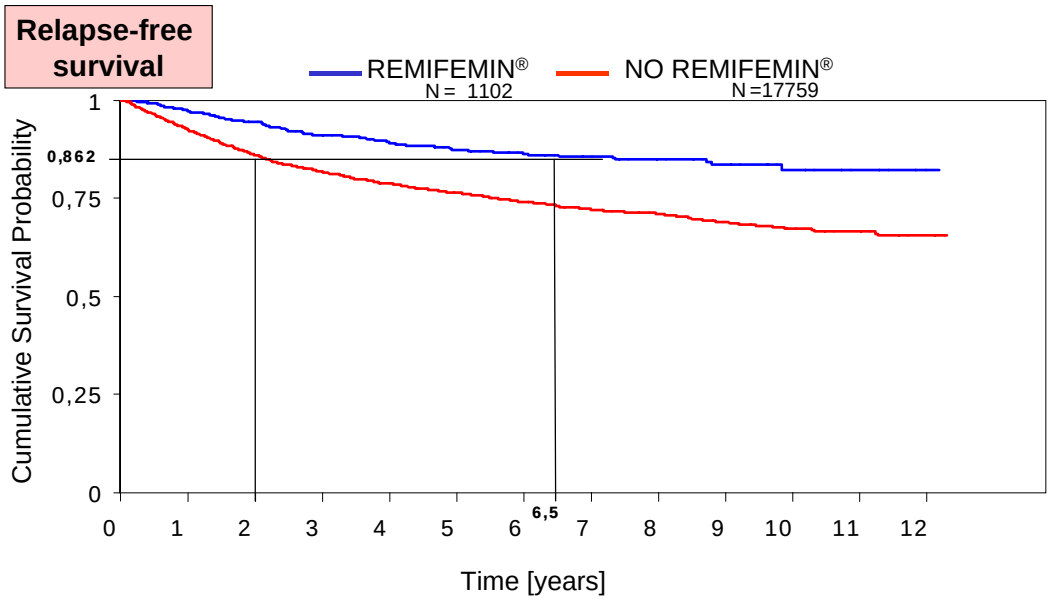

Fig. 1: Recurrence-free survival (days) in the Remifemin-group and the control (no Remifemin) group

[1] Col NF, Hirota LK, Orr RK, Erban JK, Wong JB, Lau J. Hormone Replacement Therapy After Breast Cancer: A Systematic Review and Quantitative Assessment of Risk. Journal of Clinical Oncology 2001; 19: 2357-2363.
[2] Rauthe G, de Waal JC, Engel J, Gutschow K, Höss C. Behandlungsmöglichkeiten von klimakterischen Beschwerden bei Patientinnen mit Mammakarzinom. Internist, prax. 2003; 43: 295-300.
[3] Holmberg L, Andersen H. HABITS (hormonal replacement therapy after breast cancer - is it safe?), a randomised comparison: trial stopped. The Lancet 2004; 363: 453-455.
[4] European Scientific Cooperative on Phytotherapy (ESCOP): Cimicifuga rhizoma (black cohosh). In ESCOP Monographs. Stuttgart: Thieme Verlag, 2003.
[5] Osmers R, Kraft K. Phytotherapie bei Wechseljahresbeschwerden. Pharm. Unserer Zeit 2004;22: 384-391.
[6] Boblitz N, Liske E, Wüstenberg P. Black Cohosh: Efficacy, Effect and Safety of Cimicifuga racemosa in Gynecology. Deutsche Apotheker Zeitung 2000; 140: 107-114.
[7] Zierau O, Bodinet C, Kolba S, Wulf M, Vollmer G. Antiestrogenic activities of Cimicifuga racemosa extracts. Journal of Steroid Biochemistry & Molecular Biology 2002; 80: 125-130.
[8] Dietlein G, Schröder-Bernhardi D. Use of the mediplus patient database in healthcare research. Int J Clin Pharmacol Therap 2002; 40:130-133.