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Title **Hormonal Therapies for Early Breast Cancer: Systematic Review and Economic Evaluation**

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Aim

To establish the clinical and cost effectiveness of aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane compared with tamoxifen in adjuvant treatment of early estrogen receptor-positive breast cancer in postmenopausal women with estrogen receptor-positive early-stage breast cancer.

Conclusions and results

A significant difference in overall survival was found when an unplanned anastrozole switching strategy was compared with 5 years' tamoxifen. Compared with 5 years' tamoxifen, disease-free survival was significantly improved in the primary adjuvant setting with anastrozole and letrozole, and with an exemestane switching strategy. Breast cancer recurrence was significantly improved with primary adjuvant anastrozole and letrozole, anastrozole switching, extended adjuvant anastrozole, or letrozole. AIs and tamoxifen have different side-effect profiles (eg, increases in endometrial cancer with tamoxifen, and increases in osteoporosis with AIs). Absence of tamoxifen treatment also increases the risk of hypercholesterolemia and cardiac events in women of this age.

No significant difference was found in overall health-related quality of life between standard treatment and either primary adjuvant anastrozole and extended adjuvant letrozole strategies. The cost-effectiveness results for AIs compared with tamoxifen in the primary adjuvant setting are estimated at between GBP 21 000 and GBP 32 000 per QALY. Cost-effectiveness for anastrozole and exemestane, compared with tamoxifen in the unplanned switching setting, is estimated to be GBP 23 200 and GBP 19 200 per QALY, respectively. In the extended adjuvant setting, the cost per QALY for letrozole compared with placebo is estimated to be GBP 9800. All these results are considered to be conservative. The base case assumes that the benefits of AIs over tamoxifen or placebo during the therapy period are gradually lost during the following 10 years. An alternative scenario, the 'benefits maintained' scenario, is tested in sensitivity analysis and assumes that the annual recurrence rate in both arms is the same. This reduces the cost-effectiveness ratio by over 50%, to around GBP 10 000 to 12 000, GBP 5000, and GBP 3000 in the primary adjuvant, unplanned switching, and extended adjuvant settings, respectively. Limited evidence of benefits after the therapy period suggests that the 'benefits maintained' scenario may be realistic. Results from the economic analyses in the industry submissions are generally lower than those in the authors' model and are close to or below GBP 12 000 in all 3 settings. The authors' analyses generally produce a lower estimate of QALY gain for AIs, due to the more conservative assumption on benefits, along with differences in the utility values used in the analysis.

Recommendations

Based on current data and indications, AIs can be considered clinically effective compared with standard tamoxifen treatment, but long-term effects are unclear. AIs are likely to be considered cost effective in all 3 settings, assuming that recurrence rates are the same in both arms after therapy is complete. Understanding of the long-term treatment effects on cost effectiveness is, however, incomplete.

Methods

See Executive Summary link above.

Further research/reviews required

Randomization of populations at any point other than the start of treatment programs should be discouraged in future trials. Data on AIs' impact on survival are awaited from most trials to confirm whether or not the benefits seen in disease-free survival and rates of recurrence are translated into overall survival benefit in the medium to long term. Long-term followup data on major adverse events are awaited. Evidence suggests that these adverse events do not unduly impact on the cost-effectiveness ratios. Long-term implications for the costs and benefits of AIs and tamoxifen will need to be reviewed as new information becomes available.

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