Issues to debate on the Women’s Health Initiative (WHI) study. Prescription attitudes among Belgian gynaecologists after premature discontinuation of the WHI study

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BACKGROUND: A survey was conducted in order to assess the attitude of Belgian practitioners toward HRT, after publication of the results of the ‘Women’s Health Initiative’ (WHI) study. METHODS: Using a single case of a 55-year-old woman (no particular medical history, no longer climacteric symptoms), eight clinical case records were constructed by modifying three variables: (i) the HRT type [either conjugated estrogens (CEE) 0.625 mg + medroxyprogesterone acetate (MPA) or tibolone 2.5 mg]; (ii) the HRT duration (2 years or 11 years); and (iii) the bone density result (T-score +0.5 or −1.5). One case (drawn at random) was sent to Belgian gynaecologists (n = 1374), who were asked whether they would pursue, discontinue or modify the HRT regimen. RESULTS: In total, 577 returns were obtained (42% response rate). Globally, 19.8% of the physicians would stop prescribing the CEE+MPA regimen, 19.5% would continue the same regimen, and 60.7% would prescribe another HRT type, while respectively 15.9% of them would discontinue tibolone, 76.1% would continue it and 8% would prescribe another regimen (P < 0.001). After 2 years of use, 11.7% would discontinue HRT, while 23.5% would do so after 11 years (P < 0.001). No differences in prescription rates or discontinuation rates were observed in relation to the bone density results. CONCLUSIONS: The results of this survey suggested that Belgian gynaecologists intend to continue prescribing HRT, despite the negative findings of the WHI study. When patients are using tibolone, physicians generally maintain the same regimen, but when using CEE+MPA physicians tend to prescribe another HRT regimen. Less than 25% of physicians will spontaneously discontinue HRT, even after 11 years of use.

Key words: breast cancer/HRT/questionnaire/WHI study

Introduction

In July 2002, the gynaecological community was shocked when the ‘Women’s Health Initiative’ (WHI) decided prematurely to stop its clinical trial, after having decided that the risks of hormone replacement therapy (HRT) outweighed its benefits (Writing Group for the Women’s Health Initiative Investigators, 2002). Indeed, this study found that HRT increased the risk of invasive breast cancer, heart disease, stroke and pulmonary embolism more often than it reduced the risk of osteoporosis and colorectal cancer. In view of these results, many journals and societies released editorials or new guidelines to redefine prescription attitudes of HRT (Laine, 2002; McDonough, 2002; Nelson, 2002; Schneider, 2002; Skouby, 2002; Sturdee and MacLennan, 2002; Barlow, 2003), certain ‘medical journals’ discussed more the changes in attitude that should occur (Laine, 2002; Nelson, 2002; Caren and Dluhy, 2003; Kirschstein, 2003; Rymer et al., 2003).

Do physicians adapt their HRT prescription after WHI?

A survey was conducted in order to assess the attitude of Belgian gynaecologists towards HRT after this publication. This survey evaluated whether these practitioners would discontinue, continue or adapt their prescription of HRT in relation to the type of HRT that is used, the duration of use, and the bone density measurement.

Briefly, the charts were summarized of one post-menopausal 55-year-old patient with no particular medical history who used to complain of climacteric symptoms but no longer does. From this chart, eight clinical case-types were constructed by modifying three variables: (i) the type of HRT she was using [two possibilities of either conjugated estrogens (CEE) 0.625...
mg + medroxyprogesterone acetate (MPA) or tibolone 2.5 mg; (ii) the duration of HRT use (either 2 years or 11 years); and (iii) the bone density result [a T-score of +0.5; that is, a normal bone mass or one of −1.5 (osteopenia) according to definitions given by the World Health Organization] (Report of a World Health Organization Study Group, 1994).

Every practising Belgian gynaecologist (n = 1374) received, by mail, during February 2003, one of these cases (selected at random from the eight case-types). The gynaecologists were asked: (i) whether they would pursue the same HRT regimen (closed answer, no/yes); (ii) whether they would prescribe another HRT regimen (closed answer, no/yes) and, if so, which ones (open answer); and (iii) whether the HRT would be stopped (closed answer no/yes) and, if so, whether treatments other than HRT would be prescribed (open answers). The gynaecologists were assured that their participation would remain anonymous and that the survey was not commercially motivated.

A questionnaire about demographic data was included. Statistical analysis was performed using SPSS software. Descriptive and chi-square tests were used, and a P-value < 0.05 was considered statistically significant.

Do gynaecologists consider the results of the WHI study to be applicable to a particular product or to all types of HRT?

A total of 577 returns was obtained (42% response rate) after a single mailing, and the mailing was closed after 1 month. There was no difference in response rates in relation to the eight cases. Neither was there any difference in the proportion of women to men physicians (40 versus 60%), between the responders and non-responders (mean age 47.1 ± 11.8 years), nor any difference in the distribution of the number of years of practice.

Globally, 19.8% of the physicians said they would stop prescribing the CEE+MPA regimen, 19.5% would continue the same regimen, and 60.7% would prescribe another HRT type, while respectively 15.9% would stop prescribing tibolone, 76.1% would continue it, and 8% would prescribe another regimen (Table I).

Some 11.7% of the physicians would stop prescribing HRT after 2 years of treatment, and 23.5% after 11 years (P < 0.001). Similar differences were observed for both studied HRT regimens (Table II).

No differences in prescription rates were observed in relation to the bone density results in general, nor for each HRT regimen (Table III).

In the present study, the continuation rates of prescription of two regimens (CEE+MPA or tibolone) were evaluated. The choice was made to evaluate these two regimens because they are the most often prescribed regimens, and are both orally administered, ‘non-bleeding treatments’. It was observed in this survey that the rate of interruption of HRT is not related to the type of regimen prescribed. However, the rates of continuation and modification of the HRT regimen were dramatically different. Indeed, almost 80% of women given tibolone would receive the same regimen, while about 70% of

| Table I. Numbers of physicians (%) who would continue the same HRT regimen, discontinue it or change the HRT regimen, in relation to the patient’s initial treatment (CEE+MPA versus tibolone) |
| --- | --- | --- | --- |
| Attitude | CEE+MPA | Tibolone | P |
| Discontinue HRT | 52 (19.8) | 50 (15.9) | NS |
| Continue same HRT regimen | 51 (19.5) | 239 (76.1) | <0.0001 |
| Change HRT regimen | 159 (60.7) | 25 (8.0) | <0.0001 |

Values in parentheses are percentages.
CEE = conjugated estrogens; MPA = medroxyprogesterone acetate; NS = not significant.

| Table II. Numbers of physicians (%) who would continue the same HRT regimen, discontinue it or change the HRT regimen in relation to the patient’s initial treatment and its duration of use. The statistical test applies to different duration for a similar HRT regimen |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Attitude | 2 years | 11 years | P | 2 years | 11 years | P |
| CEE+MPA | CEE+MPA | | | tibolone | tibolone | |
| Discontinuation of HRT | 19 (14.8) | 33 (24.6) | 0.047 | 14 (9.1) | 36 (22.5) | 0.001 |
| Continue same HRT regimen | 27 (21.1) | 24 (17.9) | NS | 129 (83.8) | 110 (68.7) | 0.002 |
| Change HRT regimen | 82 (64.1) | 77 (57.5) | NS | 11 (7.1) | 14 (8.8) | NS |

Values in parentheses are percentages.
CEE = conjugated estrogens; MPA = medroxyprogesterone acetate; NS = not significant.

| Table III. Numbers of physicians (%) who would continue the same HRT regimen, discontinue it or change the HRT regimen in relation to the patient’s initial treatment and the bone density measurement T-score. The statistical test applies to different T-scores for a similar HRT regimen |
| --- | --- | --- | --- | --- | --- | --- |
| Attitude | T-score = +0.5 and CEE+MPA | T-score = −1.5 and CEE+MPA | P | T-score = +0.5 and tibolone | T-score = −1.5 and tibolone | P |
| Stop HRT | 27 (21.3) | 25 (18.5) | NS | 28 (19.3) | 22 (13) | NS |
| Continue same HRT regimen | 30 (23.6) | 21 (15.6) | NS | 108 (74.5) | 131 (77.5) | NS |
| Change HRT regimen | 70 (55.1) | 89 (65.9) | NS | 9 (6.2) | 16 (9.5) | NS |

Values in parentheses are percentages.
CEE = conjugated estrogens; MPA = medroxyprogesterone acetate; NS = not significant.
women using CEE+MPA would receive another HRT regimen. These results suggested that the Belgian gynaecologists believed the results of the WHI study to be more applicable to a particular product (CEE and/or MPA) than to HRT per se. In the present study, the gynaecologists were not asked to motivate their choice in order not to influence their decision. Nevertheless, when gynaecologists were interviewed informally about their attitudes, different arguments were forwarded. Many gynaecologists considered that other regimens, including different progestins, other routes of administration or lower doses are still useful. These arguments found their origin in publications which assessed that, using progestins other than MPA, the lipid profile or the insulin metabolism may be less altered, or that during oral but not transdermal HRT, C-reactive proteins (CRP) have been reported to increase (Langer, 2000; Decensi et al., 2002; Vongpatanasin et al., 2003). Likewise, interpretations were also sustained by the fact that the evaluation of unopposed estrogen versus placebo in the WHI study has not ended. Furthermore, preparations which deliver a minimal amount of estrogen are available or under development, and it has been reported that these doses are sufficient for both controlling climacteric symptoms and avoiding bone density loss (Lees and Stevenson, 2001; Lindsay et al., 2002; Rice, 2002). Alternatively, physicians may also find that tibolone is different from the classical estro-progestin HRT and has a less deleterious effect on breast tissue. Arguments for this hypothesis, suggesting that tibolone exerts a tissue-specific effect (unlike estrogen and progestin) have also been found in the recent literature, are largely diffused at meetings, and are aggressively defended by representatives of the pharmaceutical industry (Colacurci et al., 1998; Ginsburg and Prelevic, 2001; Kloosterboer, 2001). Physicians, especially in Europe, often claim that the ‘bad cardiovascular’ results of the WHI may be due to the wrong ‘choice of drug’, while some also add ‘in the wrong population’.

Finally, some gynaecologists have ‘psychological difficulties’ in discontinuing medication that they have prescribed often for many years, especially to patients who are not asking to stop their regimen and may feel well while using it. These hypotheses may also explain why HRT discontinuation remained very low after 2 years of HRT use (<15%) and even after 11 years of HRT use (<25%). The result of the bone density investigations had no significant effect on the (dis)continuation rates, which suggested that the physicians’ main reason for maintaining patients under treatment was not osteoporosis prevention. Nonetheless, it should be noted that those practitioners who would stop HRT also more frequently prescribed calcium associated with vitamin D (70–78% of cases; data not shown). It is also possible that some physicians believe that HRT improves the quality of life and should therefore be maintained for long periods.

Some limitations of the present study must be considered. The response rate obtained was low, and it was not clear whether these results could be extrapolated to physicians other than those who answered the questionnaire. Despite this, the results observed were also in concordance with the decrease in sales by almost 40% of ‘conjugated estrogens 0.625 mg + medroxyprogesterone acetate’ that has been noted in Belgium during the year following the first WHI results, whilst on the other hand there was an increase of more than 10% in tibolone use. It should also be noted that, since the study was conducted, additional reports have appeared in the fields of breast cancer, stroke, cognitive function, dementia and quality of life, all from the team of the WHI study, that reinforce the negative opinion concerning long-duration combined HRT (Chlebowski et al., 2003; Hays et al., 2003; Rapp et al., 2003; Shumaker et al., 2003; Wasserman-Smoller et al., 2003). The attitude of Belgian physicians has not been reassessed since publication of these data, however.

In summary, this survey reveals that Belgian gynaecologists who are confronted with patients who became asymptomatic while using HRT, will generally continue to prescribe HRT, despite the negative findings of the WHI study. When patients are using CEE+MPA, physicians tend to prescribe another HRT regimen, but when patients use another regimen such as tibolone, physicians generally tend to maintain the same regimen. The real clinical setting of a patient informed (frightened!) by the lay press or by another health provider may however result in a different scenario. If gynaecologists intend to maintain their patients on HRT, then incomprehension and possibly distrust may arise. Gynaecologists should be aware of this situation, in addition to the potential dangers of HRT.

References

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