Hormonal treatment for male-pattern hair loss: implications for cancer of the prostate?

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Introduction

One of the sad reminders of advancing years is male-pattern hair loss (MPHL). Not only is a highly reflective pate the source of many cruel jokes, but the condition is also associated with depression, suicide and a lack of self-esteem, as well as perceived discrimination [1,2]. Therefore it is hardly surprising that research into MPHL has been targeted by several pharmaceutical companies worldwide for many years, as a panacea for this condition would certainly be in great demand.

Since early March 2002, finasteride 1 mg (Propecia™, Merck Sharp and Dohme) has been available in the UK to patients whose doctors are prepared to prescribe it privately. Predictably, this launch has achieved much media publicity. With the first 5-year study having recently appeared in a medical journal [3], encouraging results have been reported in treating MPHL and this is bound to further fuel the demand for finasteride 1 mg. Herein we discuss the possible implications of manipulating testosterone metabolism in MPHL in relation to prostate cancer.

Current therapy for MPHL

In treating MPHL numerous therapies have been tried over the years, both surgical and medical, with varying degrees of success. The first work describing hair transplantation in humans is usually attributed to Dr Norman Orentreich, a New York dermatologist who, in the 1950s took 4-mm grafts from the occipital region and reimplanted them into the hair-depleted areas. The hair within the newly implanted grafts generally falls out within a short period after implantation, but new hair will typically grow in the grafts within 3 months. The transplanted graft retains the occipital characteristic of resilience and will therefore not be as prone to loss as the surrounding ungrafted hairs. Unfortunately, the grafted 'plugs' can appear raised in relation to the adjacent tissue and give the patient's scalp a 'doll's head' appearance, with precisely laid rows of grafts. The cosmetic appearance may be less than desirable and the surgically disfigured scalp may attract much more curiosity than would an innocuous bald spot.

In recent years, the surgery for MPHL has developed into micrografting, with smaller grafts being used to give a more acceptable appearance. In addition, techniques have been developed for individual hair placements, especially to help achieve a natural hairline. Other surgical treatments that are available include balloon expansion with skin excision, skin grafting and pedicle transfer.

Until recently, minoxidil was the only licensed drug treatment for MPHL in the UK [4]. When minoxidil was first launched as an oral vasodilatory antihypertensive, it soon became apparent that hypertrichosis was a side-effect in many patients. The mode of action in MPHL is thought to be primarily vascular rather than hormonal. Given as a 2% or 5% topical solution which is applied daily to the scalp, the patient is faced with the prospect of lifelong applications of a solution, which will usually only cause limited re-growth and which, when stopped, will result in the loss of the new hair [4].

Other non-surgical options include various forms of hairpieces, toupees and wigs, which are widely available but may give the patient an unnatural appearance. (Perhaps it is only 'the bad ones' that appear unnatural, whereas 'the good ones' are not noticeable?). Isolated cases of 'miracle cures' using cow saliva and cow dung have, unsurprisingly, not gained widespread acceptance.

Finasteride as therapy for MPHL

The complete mechanism behind MPHL remains unresolved, although it is increasingly accepted that DHT sensitivity in scalp hairs, along with a familial predisposition to MPHL, are the two major factors [5,6].

Finasteride has been used for several years in the treatment of BOO caused by BPH; in this context, it is given as...
α-reductase, the enzyme that converts testosterone to DHT. There are two isomeric forms of 5α-reductase, with the type I isomer found principally in skin [7,8], including the scalp, whereas type II is found in hair follicles and urogenital tissue, including the prostate [7,9]; finasteride is a type II 5α-reductase inhibitor [10].

Numerous studies have shown that finasteride 5 mg daily will result in a decrease in prostatic volume over a period of months, and will lower the PSA level of the treated patient. For instance, The Finasteride Study Group [11] reported a mean decrease in prostate volume at 12 months of 19% in men treated with finasteride 5 mg daily; they also noted a mean reduction in PSA of 50%.

The Proscar™ Long-term Efficacy and Safety Study (PLESS) assessed 3040 men over a 4-year period and concluded that the PSA value should be doubled for men taking finasteride 5 mg, to give an ‘actual’ PSA value [12]. Similar findings and recommendations have been made from other studies [13,14].

Finasteride 1 mg was first launched in 1998 (Propecia) as a therapeutic option for MPHL. A licence for the application of Propecia in treating MPHL was initially granted in the UK on 20 September 1999 (Department of Health; http://www.doh.gov.uk/) to Merck, Sharp and Dohme. However, the drug did not appear on Schedule 10 of the NHS (General Medical Services) Regulations 1992, and in Scotland under Schedule 10 of the (General Medical Services) (Scotland) Regulations 1995, until 1 August 2000. In 1999, the UK government predicted that demand would be high, with an estimated cost to the NHS of £6–32 million; after due consideration, the Department of Health declared that this would be excessive in the current NHS climate, thereby explaining why this medication would not be available on NHS prescription.

The drug is officially currently available in over 40 countries, but checking the Internet showed that numerous web-based companies have noted the demand for finasteride 1 mg and are therefore supplying a worldwide audience. Many of these companies are selling the cheaper (relatively) finasteride 5 mg as a treatment for MPHL and then advising their customers to cut the tablets into 1 mg-sized portions.

Two 1-year randomized, double-blind trials of 1553 men have been conducted by Kaufman et al. [10]. Of these men, 1215 continued for a 1-year trial extension; 83% of treated men had no further hair loss (vs 28% on placebo) by subjective and objective assessments, and clinically significant increased hair growth patterns occurred in 66% of treated patients (vs 7% on placebo). The first 5-year study was recently published by Kaufman et al. [3] on behalf of the same research group, and also showed very encouraging and sustained results at 5 years.

Discussion

According to UK Government statistics prostate cancer is currently the second largest cause of cancer deaths in men in the UK; in 1997 ~8500 men died from prostate cancer and 18 300 men were newly diagnosed. Projected values suggest that by 2020 prostate cancer will be the largest cause of death from cancer in UK men.

Several studies, including the Prostate Cancer Prevention Trial (PCPT) funded by the USA National Cancer Institute, are assessing the possible chemoprotective role of finasteride 5 mg in prostate cancer. This study will achieve its primary endpoint in October 2004 [15]. If studies such as the PCPT confirm that there is a definite protective role with finasteride 5 mg, then the chemoprotective role of finasteride 1 mg must be investigated further.

The Government estimates that there are 5.7 5 million men in the UK with MPHL who would be suitable for treatment with finasteride 1 mg. This is ~30% of the adult male population in the UK. Given the much larger market that could therefore be supplied with finasteride 1 mg, the demographics of prostate cancer could potentially alter as a result of the widespread prescription of this medication; for instance, the presenting age at diagnosis may be raised and the number of actual cases may decrease.

The extent to which the 1 mg dose of finasteride affects PSA levels remains a matter of debate. The manufacturers of finasteride 1 mg accept that PSA concentrations need to be ‘considered during treatment with Propecia’ and recommend in their Summary of Product Characteristics (SPC, Merck Sharp and Dohme, January 2001) that estimates of PSA levels should be doubled for patients on finasteride 1 mg. This SPC states that, in clinical studies in men aged 18–41 years, Propecia reduced the mean value of serum PSA from 0.7 ng/mL at baseline to 0.5 ng/mL at 12 months. However, not only does this advice reflect on an age group that is generally unaffected by pathological PSA values, but to double 0.5 ng/mL would give 1.0 ng/mL and not 0.7 ng/mL thereby over-estimating the ‘actual’ PSA by 43% ((1.0–0.7)/0.7×100%).

The Finasteride 1 mg PSA Study Group [16] conducted a 48-week randomized, placebo-controlled study of 344 men aged 40–60 years with androgenic alopecia and no known prostatic disorders. They concluded that in men aged 40–50 years the mean reduction of PSA was 40% and in those aged 50–60 years the reduction was 50%. Overall, this gave a mean PSA reduction of 42%. In 1992, Gormley et al. [11] described a mean reduction in PSA of 48% at 1 year for men treated with finasteride 1 mg. However, in the 2-year study by Kaufman et al. [10] of men taking finasteride 1 mg (cited in the SPC), the serum PSA value decreased by ~30% at 1 years (from 0.7 to 0.5 ng/mL). The results of their subsequent 5-year study were published recently and show that patients treated with
finasteride 1 mg had a mean PSA at 5 years of 0.5 ng/mL, compared with a baseline of 0.7 ng/mL [3], i.e. the mean reduction in PSA at 5 years was identical to that occurring after 1 year.

There is clearly a lack of agreement about PSA reduction by finasteride 1 mg and this could potentially devalue the PSA assay for patients on this medication; any PSA value that is corrected to give an actual value becomes educated guesswork. Indeed, over-multiplying a measured PSA to obtain an actual PSA value in these patients may lead to inappropriate anxiety and investigations, with the associated inherent morbidity, e.g. discomfort, haemorrhage and infection from prostatic biopsy. Equally, by under-multiplying the PSA in patients on finasteride 1 mg, a false sense of security may prevail. The number of ‘missed’ cases may increase, as the assistance from PSA in making the diagnosis may be lost, and PSA monitoring for treated patients may become misleading and unrepresentative.

Certainly, there is reassurance in the findings of PLESS which suggest that finasteride 5 mg does not hinder the detection rate of prostate cancer [12]. However, as finasteride 1 mg is a different dose which is likely to be used in a different age group, potentially by far more patients and for much longer, the issue of altered detection rate with finasteride 1 mg may not be fully known for years. By decreasing the volume of the gland with finasteride 1 mg, could the detection rate from prostatic biopsy actually be improved, as the volume of tumour relative to gland could be increased?

The possible requirement for measuring baseline PSA before treating MPHL with finasteride 1 mg may have to be discussed with the patient, as would potential implications for the diagnosis and monitoring of prostate cancer in later years. Any doctor or nurse involved in dispensing finasteride 1 mg would have to be fully informed of probable PSA changes and concerns about prostate cancer, not just for reasons of ‘good clinical practice’ but also because failure to be aware of these issues may well have medicolegal implications.

Conclusions

The idea of taking a pill to conquer MPHL is attractive and will almost certainly meet with great demand from a grateful audience of men. This is surely a welcome development. However, the possible implications for prostate cancer diagnosis and management may not be known for years, and this must be entirely appreciated by both the patient and the doctor when prescribing this medication.

PSA assays are usually given to one or two decimal places; the danger of losing this accuracy by converting the result to a ‘best-guess’ approximation has to be fully considered and is not acceptable as good science. Long-term studies into PSA reduction by finasteride 1 mg are lacking but are clearly warranted; many of the current studies into PSA changes are relatively short-term and funded by the pharmaceutical industry, therefore raising the issue of possible bias. Regular symptomatic enquiry, with a DRE of the prostate and long-term monitoring of PSA for patients on finasteride 1 mg, should be considered until such details are established.

References

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Abbreviations: MPHL, male-pattern hair loss; PLESS, Proscar™ Long-term Efficacy and Safety Study; PCPT, Prostate Cancer Prevention Trial; SPC, Summary of Product Characteristics.