

## BRIEF REPORT

# Combination therapy with finasteride and low-dose dutasteride in the treatment of androgenetic alopecia

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### ABSTRACT

We report on a 47-year-old man who was initially treated with finasteride for androgenetic alopecia. Despite continuous treatment, after year 4 his hair density was not as good as at year 2, and low-dose dutasteride at 0.5 mg/week was added to the finasteride therapy. This resulted in a dramatic increase in his hair density, demonstrating that combined therapy with finasteride and dutasteride can improve hair density in patients already taking finasteride.

**Key words:** androgenetic alopecia, dutasteride, finasteride, male pattern hair loss.

### INTRODUCTION

Androgenetic alopecia (AGA) or male-pattern hair loss, results in the progressive conversion of scalp terminal hair into vellus hair over the frontal and vertex scalp in genetically susceptible men.<sup>1</sup> A major enzyme in the pathophysiology of AGA is 5 $\alpha$  reductase, which catalyses the conversion of testosterone to dihydrotestosterone (DHT), an androgen strongly implicated in AGA.<sup>1</sup> Inhibitors of 5 $\alpha$  reductase, including finasteride and dutasteride, are effective in the treatment of AGA.

Finasteride is a type II 5 $\alpha$  reductase inhibitor approved for the treatment of AGA. Its efficacy has been demonstrated in several large randomised, phase III trials.<sup>2,3</sup> Hair regrowth occurs in approximately two-thirds of men. Maximal hair regrowth is seen within 2 years and declines slightly thereafter. At year 5 the hair density is higher than the year 0 baseline but lower than the 2-year peak. In contrast, the placebo group continue to lose hair.<sup>4</sup>

Men who responded initially to finasteride, but who later notice a resumption of hair loss may present for additional treatment. Dutasteride is a dual (type I and II) 5 $\alpha$  reductase inhibitor that has shown superior efficacy to finasteride in the treatment of AGA.<sup>5</sup>

### METHOD

A 47-year-old man presented with a 2-year history of hair loss, particularly over the vertex, which was clinically consistent with AGA. His past history included asthma. He was not taking regular medications. The patient was commenced on 1 mg of oral finasteride daily, and baseline photographs were taken (Fig. 1a). On review 6 months later, he had a good response on patient and physician assessment, as well as in comparison with the baseline photographs (Fig. 1b). There were no reported side-effects to finasteride.

Over the next 4 years, the patient continued to respond to finasteride, as assessed by the physician, patient and serial photography. At year 4 his response to finasteride had begun to decline and a reduction in his hair density was noted (Fig. 1c).

Dutasteride was commenced at a dose of 0.5 mg/week while his finasteride was continued. There were no side-effects from this combination treatment. Within 3 months, there was a dramatic increase in his hair density, with the vertex showing almost complete hair regrowth (Fig. 1d).

### DISCUSSION

Hair growth in most body sites is mediated by DHT, a potent metabolite of testosterone. DHT is converted to testosterone by the enzyme 5 $\alpha$  reductase. There are three isoforms of the enzyme (types I, II and III) which are encoded by separate genes, and which differ in the amount present in various tissues and location.<sup>6</sup> In the skin, type I is mainly present in

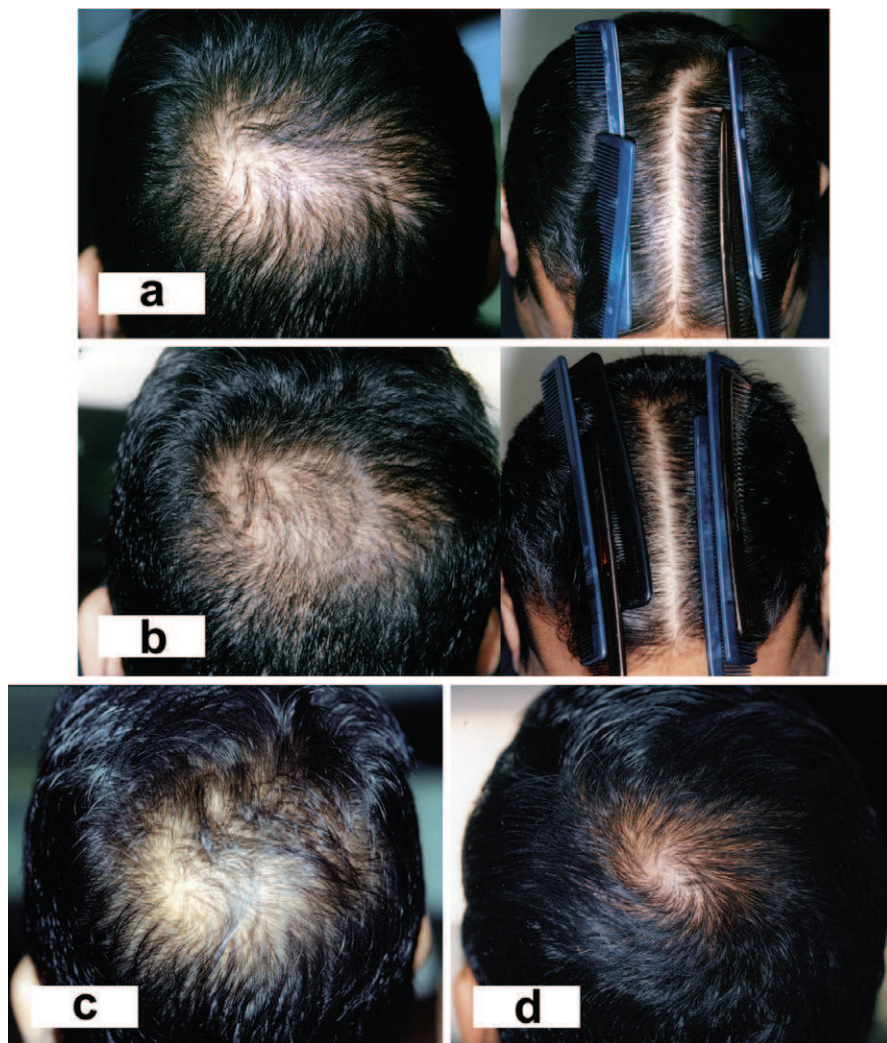
### Abbreviations:

AGA	androgenetic alopecia
BPH	benign prostatic hyperplasia
DHT	dihydrotestosterone
TGA	Therapeutic Goods Administration

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**Figure 1** Clinical photographs of patient showing (a) baseline pretreatment, (b) good response after 6 months of finasteride therapy, (c) reduction in hair density after 4 years of continuous finasteride therapy, and (d) hair regrowth after addition of low-dose dutasteride to finasteride therapy.

sebaceous and sweat glands, and type II predominates in genital skin, beard and scalp hair follicles.<sup>6</sup> In the follicles it is found predominately in the outer root sheath and, to a lesser extent, the inner root sheath, but not in the dermal papilla or sebaceous gland.<sup>7</sup> Type III protein is expressed ubiquitously throughout the dermis and epidermis and the expression of  $5\alpha$  reductase type III is much higher in the dermis than types I and II.<sup>8</sup>

Dutasteride inhibits both type I and II  $5\alpha$  reductase, and was approved by the Australian Therapeutic Goods Administration (TGA) for the treatment of symptomatic benign prostatic hyperplasia (BPH) in 2002. It is more potent than finasteride in inhibiting  $5\alpha$  reductase, being thrice as potent in blocking the type II enzyme and more than 100-fold as potent in blocking the type I enzyme.<sup>9</sup> Finasteride decreases serum DHT by 73%, while dutasteride decreases it by 92%.<sup>6</sup>

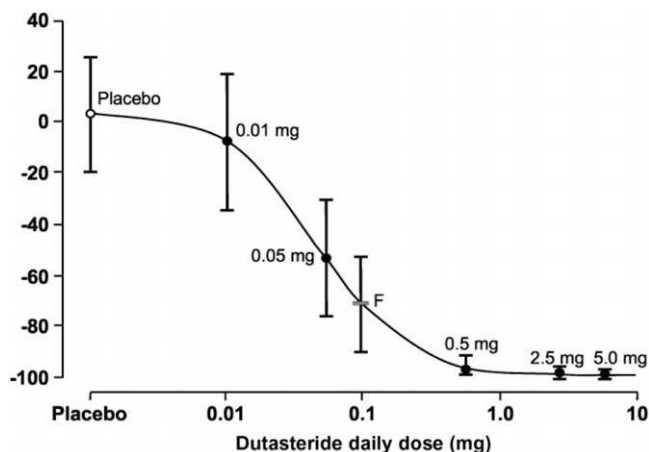
Dutasteride decreases intraprostatic DHT by 99%. This near maximal suppression of intraprostatic DHT indicates that the development of a triple  $5\alpha$  reductase inhibitor may not be necessary for BPH.<sup>6</sup> With respect to AGA, the best predictor of scalp hair regrowth is scalp DHT. Scalp DHT is

reduced by only 41% with finasteride and 51% with dutasteride.<sup>10</sup> This suggests a triple  $5\alpha$  reductase inhibitor could be useful in AGA. Interestingly finasteride is also a potent inhibitor of type III  $5\alpha$  reductase. The half maximal inhibitory concentration for finasteride for the type III isoenzyme is approximately fourfold lower than for the type II isoenzyme.<sup>6</sup>

Our patient's experience shows that combination therapy with finasteride and low-dose dutasteride is more effective in treating AGA than finasteride alone. Because of the low dose used this is likely to be due to an additional blockade of the type I isoenzyme rather than the enhancement of the type II or III enzyme blockade.

We chose to continue finasteride treatment in this patient as he was tolerating it well and without any side-effects. It had worked initially and it provided a good blockade of type II and III isoenzymes. We chose to add dutasteride to his treatment specifically for type I isoenzyme blockade.

We used a low dose of dutasteride because of its relative selectivity for type I isoenzyme and intermittent dosing because of its long pharmacological and biological half-life.



**Figure 2** The dose-response relationship of suppression of dihydrotestosterone serum levels with dutasteride. (Reproduced with permission from the Endocrine Society)

Dutasteride has a terminal elimination half-life of 5 weeks<sup>11</sup> and in addition, binds irreversibly to the 5  $\alpha$  reductase enzymes and therefore has an extremely long biological half-life.<sup>11</sup> We used 0.5 mg/week of dutasteride, which is just under 0.1 mg/day. Figure 2<sup>9</sup> shows that this dose can produce DHT suppression. Dutasteride weekly dosing produces serum levels similar to daily and monthly dosing (pers. comm.).

Currently, dutasteride is approved by the FDA and TGA only for the treatment of BPH. Phase III trials for the treatment of AGA have recently been conducted. The main safety concern with dutasteride is its effect on sexual function. However, 4 year follow up of phase III trials in BPH have shown that dutasteride 0.5 mg daily is generally well tolerated, with the incidence of common sexual side-effects that is low and tends to decrease over time.<sup>12</sup>

The functional role in the skin of type III 5 $\alpha$  reductase in reducing steroid substrates has not yet been elucidated.<sup>15</sup> While it is interesting to speculate that the enhanced efficacy in this patient was due to a triple blockage of the 5 $\alpha$  reductase enzyme leading to lower scalp DHT concentrations, we cannot answer this question as we did not measure the scalp DHT in this patient. It is also possible that simply stopping the finasteride and commencing dutasteride monotherapy might have had the same effect.

## CONCLUSION

Some men with AGA who have been treated with finasteride for many years may find that the beneficial effects of the

treatment wane. The addition of intermittent low-dose dutasteride to their ongoing finasteride treatment could increase hair regrowth in this group of patients.

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