Original Investigation

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Adverse Event Reporting in Clinical Trials of Finasteride for Androgenic AlopeciaA Meta-analysis

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Abstract

Importance Two meta-analyses conclude that finasteride treatment of androgenic alopecia (AGA) is safe but do not assess quality of safety reporting.

Objective To assess safety reporting for clinical trial reports of finasteride for AGA.

Data Sources MEDLINE, ClinicalTrials.gov, and a clinical data repository for an academic medical center.

Study Selection Published clinical trial reports for finasteride treatment of AGA.

Data Extraction and Synthesis For each trial, we assessed quality of adverse event reporting, extracted the number and type of adverse events in treatment and placebo groups, and assessed duration of safety evaluation and adequacy of blinding. Two observers independently extracted the data; differences were resolved by consensus. We assessed generalizability in a large cohort of men prescribed finasteride, 1.25 mg/d or less, by assessing for eligibility in the finasteride-AGA pivotal trials.

Main Outcomes and Measures Quality was assessed as adequate, partially adequate, inadequate, or no events reported. We used funnel plots of the hazard ratio to assess bias.

Results Of 34 clinical trials, none had adequate safety reporting, 19 were partially adequate, 12 were inadequate, and 3 reported no adverse events. Funnel plots were asymmetric with a bias toward lower odds ratio for sexual adverse effects, suggesting systematic underdetection. No reports assessed adequacy of blinding, 18 (53%) disclosed conflicts of interest, and 19 (56%) received funding from the manufacturer. Duration of drug safety evaluation was 1 year or less for 26 of 34 trials (76%). Of 5704 men in the clinical data repository who were treated for AGA with finasteride, 1.25 mg/d or less, for AGA, only 31% met inclusion criteria for the pivotal trials referenced in the manufacturer's full prescribing information and 33% took finasteride for more than 1 year.

Conclusions and Relevance Available toxicity information from clinical trials of finasteride in men with AGA is very limited, is of poor quality, and seems to be systematically biased. In a cohort of men prescribed finasteride for routine treatment of AGA, most would have been excluded from the pivotal studies that supported US Food and Drug Administration approval for AGA. Published reports of clinical trials provide insufficient information to establish the safety profile for finasteride in the treatment of AGA.

Introduction

Androgenic alopecia (AGA) is characterized by vertex balding of the scalp and recession of the temporal hairline due to 5α-dihydrotestosterone (5α-DHT)–dependent miniaturization of hair follicles. About 70% of men develop AGA. Some men with AGA experience adverse psychosocial effects and reduced quality of life, particularly those with early age at onset.[1] The development of finasteride for clinical use was prompted by the observation that male pseudohermaphrodites do not develop prostatic hyperplasia or AGA.[2] Male pseudohermaphrodites have a mutation of the gene encoding 5α-reductase 2, a global defect in C_{19} and C_{21} 5α-metabolism,[3,4] impaired conversion of testosterone to 5α-DHT, and a reduced 5α-DHT:testosterone ratio—with varying degrees of genital ambiguity at birth.[2,5] Pseudohermaphrodites are often raised as girls but unexpectedly virilize at puberty, with partial masculinization of external genitalia.[2] Finasteride is a 5α-reductase inhibitor that reduces serum 5α-DHT by 70% at doses of either 1 mg or 5 mg,[6,7] inducing a sex steroid profile "strikingly similar to that of pseudohermaphrodites."[8(p777)] Implicit in the use of finasteride is the assumption that inhibiting formation of 5α-DHT will not interfere with maintenance of the structure or function of male reproductive organs, despite the expression of 5α-reductase 2 in these organs[9] and despite the overexpression of nuclear androgen receptor in men with persistent sexual dysfunction after discontinuation of finasteride.[10]

One meta-analysis of controlled trials of finasteride for AGA found "no significant difference between active treatment and placebo for the outcome global sexual disturbance"[11(p160)] and asserted that "controlled–clinical trial data shows a low incidence of sexual side effects that resolve on treatment."[11(p160)] A second meta-analysis found that, "the only adverse effect that was significantly more frequent with finasteride therapy in comparison to placebo treatment was erectile dysfunction"[12(p1149)] and that only "1 of every 80 patients treated will experience erectile dysfunction."[12(p1149)] Neither analysis assesses the quality of adverse event reporting nor evaluates generalizability to clinical practice. Recent reports describe that impotence, loss of libido,[13,14] low androgen levels, and severe oligospermia[15] may persist long after discontinuation of finasteride at a dosage of 1.25 mg/d or less. Yet, a medical literature review of the use of finasteride for AGA concludes that finasteride is safe for AGA and notes that "permanent sexual adverse events have yet to be established in higher quality studies, such as randomized controlled trials."[16(p493)] Although clinical trial reports are generally considered the best source of information about the efficacy and safety of drug therapy, a recent meta-analysis found that 35% of published reanalyses of clinical trial data made conclusions that were different from those in the original published report.[17] Accordingly, we evaluated the quality and relevance of adverse event reporting for published clinical trials of finasteride for AGA.

Methods

We searched Medline for reports of clinical trials of oral finasteride for treatment of AGA in men using the keywords "alopecia," "androgenic alopecia," "5α–reductase inhibitor," "finasteride," and "Propecia," identified 353 items, and manually assessed each item for content, relevance, and duplication, yielding 34 unique clinical trial reports.[6,7,18-49] We searched ClinicalTrials.gov using the

keyword “finasteride” and found no nonduplicative reports. We evaluated each of the 34 reports of finasteride AGA trials for study design, drug dosage, sample size, average age, study duration, quality of adverse event reporting, adequacy of blinding, treatment indication, withdrawal rate, inclusion and exclusion criteria, conflicts of interest, and funding source. We determined odds ratios for sexual dysfunction, decreased libido, and impotence for those studies with both a finasteride arm and a placebo arm for which the requisite information was available. Two observers (I.A. and T.K.) independently extracted the data; differences were resolved by consensus.

We classified adequacy of blinding as “not applicable” for studies with 1 arm, as “yes” for studies reporting assessment of adequacy of blinding, and as “unknown” for those not reporting assessment of adequacy of blinding. We scored drug safety reporting for each report using the adverse event reporting quality scale of Ioannidis and Lau[50] as “adequate,” “partially adequate,” or “inadequate.” Reports that explicitly stated that no adverse events had occurred were scored as “none.” Trials were classified as having adequate quality of adverse event reporting if they used an explicit toxicity scale to grade adverse event severity and reported numbers and/or rates of occurrence for each specific type of adverse event per study arm. Trials were classified as having partially adequate quality of adverse event reporting if they failed to distinguish reports of severe toxicity from reports of moderate toxicity or otherwise did not meet criteria for the adequate or inadequate categories. Trials were classified as having inadequate quality of adverse event reporting if they did not enumerate specific types of adverse events, provided only generic statements, or omitted comment entirely.

To assess generalizability, we evaluated eligibility for the 3 manufacturer-sponsored trials[26,27,32] referenced in the Clinical Studies section of the full prescribing information for finasteride, 1 mg, using as our data source the Northwestern University Enterprise Data Warehouse, a clinical data repository of ambulatory and hospitalized patients, providing laboratory data and diagnosis codes from 1992 through 2013 and comprehensive electronic medical record data from January 2001 through September 2013. We applied a 1.25-mg dose threshold because tablet splitting of the 5-mg dose was widely used as a cost-saving measure. We identified all *International Classification of Diseases, Ninth Revision (ICD-9)* codes for the cohort of men prescribed finasteride, 1.25 mg/d or less, in the clinical data repository and identified 345 exclusionary *ICD-9* codes based on the exclusion criteria for the 3 trials[26,27,32] referenced in the full prescribing information for men younger than 42 years. Principal exclusion criteria included significant abnormalities on screening physical examination or laboratory evaluation.[26,27]

The Northwestern University institutional review board granted approval for conduct of this study.

Results

Of 34 articles, none had adequate safety reporting, 19 (56%) had partially adequate reporting, 12 (35%) had inadequate safety reporting, and 3 (9%) reported that no adverse events occurred (Table 1). Of 25 clinical trial reports with a control arm, none reported on adequacy of blinding. The 34 publications reported data for 9751 unique human participants: 18 articles (53%) disclosed that authors had conflicts of interest, 19 articles (56%) reported funding by a pharmaceutical manufacturer of finasteride, and 12 articles (35%) did not disclose a funding source; 26 trials (76%) had a study duration of 1 year or less. The median number of participants assigned to a finasteride treatment arm was 68 (range, 8-3177 participants); 29 trials evaluated a finasteride dose of 1 mg, 2 studies evaluated doses of both 1 and 5 mg, and 3 studies evaluated a dose of 5 mg. The mean age of participants was 35.5 years across all studies. Nonsexual adverse drug events were not reported in 28 articles. One report[40] specifically evaluated depression, finding a clinically and statistically significant increase in Beck Depression Inventory Scores after exposure to finasteride, but did not adequately assess adverse effects other than depression. Another 5 studies[7,27,33,35,44] reported nonsexual adverse drug events, including increased body hair, gynecomastia, elevated liver function tests, elevated cholesterol levels, and mood disorder.

Sufficient information was available to calculate an odds ratio of sexual dysfunction for 7 studies[7,26,29,32,37,46,47] (21%), of decreased libido for 12 studies[6,7,18,24,26,27,29,31,32,35,39,47] (35%), and of impotence for 7 studies[7,24,26,27,32,35,47] (24%). The Figure shows funnel plots of odds ratios vs sample size of the finasteride arm for these outcomes. All 3 funnel plots are asymmetric with a bias toward lower odds ratios, suggesting possible underdetection or underreporting of sexual adverse effects in these trials, perhaps owing to publication bias. Alternatively, the larger clinical trials may have differed systematically from the others.

Of the 5704 men in the clinical data set who were prescribed finasteride at doses of 1.25 mg or less daily, 69% would have been excluded from the clinical trials that supported the new drug application for finasteride, 1 mg (Table 2). Also, while 26 of the 34 clinical trials had a study duration of 1 year or less, 33% of the men in the clinical data repository had more than 1 year of exposure to finasteride, and 12% had more than 3 years of exposure to finasteride.

Discussion

Of 34 studies, none met the criteria of Ioannidis and Lau[50] for adequate safety reporting. Most provided no description of the duration or severity of signs or symptoms of sexual dysfunction and failed to distinguish between mild, reversible sexual dysfunction and severe, permanent sexual dysfunction. Also, given that some participants randomized to finasteride would likely have noticed cessation or reversal of balding and that adverse event assessments were based on participant reports, the lack of assessment of adequacy of blinding is a serious flaw in the reporting of these 34 clinical trials. Furthermore, lack of generalizability represents another serious limitation of the available clinical trial data because analysis of a large cohort of men actually taking finasteride at doses of 1.25 mg/d or less per routine care showed that 69% of such men met exclusion criteria for the 3 clinical trials that supported FDA approval of finasteride, 1 mg daily, for AGA.

Conclusions

Clinical trials provide the “…best (and only) opportunity for assessing the frequency and severity of common side effects from a new medication in a controlled setting.”[50(p442)] This opportunity to identify and characterize drug toxicity may be lost when investigators do not use validated, effective methods for detecting adverse events, grading their severity, and evaluating causality. Remarkably, the sole study[40] that used validated methods to assess depression in men found a strong association between finasteride exposure and depression, while only 1 of the remaining 33 trials reports “mood disorder” as an adverse event and determined this to be not significant. Clinicians depend on clinical trial reports as the definitive source of information on drug toxicity. One might reasonably expect that 34 studies and 2 meta-analyses would be adequate to establish the rate of finasteride adverse effects in AGA, yet this does not seem to be the case.

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