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# Editorial Review of "Comparison of Phytotherapy (Permixon®) with Finasteride in the Treatment of Benign Prostate Hyperplasia: A Randomized International Study of 1098 Patients"

The presentation of this trial in a satellite meeting of the Third International Consultation on BPH in Monaco, June 26–29, 1995, provoked a lot of interactive discussion between the presenting panel and BPH experts in the audience. We are sure that, in view of the sensitivity of the issue on the efficacy of phytotherapy in the medical treatment of BPH and the assertiveness of a number of colleagues on the subject, this publication will certainly provoke nudges of approval or grunts of disapproval from our readership [1].

For the background of the discussion we have to go back to the First International Consultation in 1991 where the Scientific Committee proposed the standardization of the evaluation of BPH pharmacological management. To summarize, it was stated that future studies should meet the clinical research criteria and response criteria proposed by the International Consultation on BPH. All trials were expected to be randomized, controlled, and to include a follow-up of at least one year, following expected time of onset of response. The trials should be conducted under double-blind conditions and stratified with regard to prognostic factors of treatment outcome. It was further stated that pharmacological treatments for BPH must be compared with an appropriate control and that the most appropriate control is a placebo treated group. Last but not least, all trials should include an analysis of the morbidity of the pharmacological management.

In 1991, it was felt that the only approved medical treatment by these rules of standardization would apply to alphablockers and 5-α reductase inhibitors. It was clear from the beginning however, that phytotherapeutic agents, widely used in Europe for the treatment of BPH, would be put to the test to meet this challenge. It was the hope of the Scientific Committee that the randomized studies would be properly performed and would give a possible lead to the rationale and mode of action which is still lacking in most phytotherapeutic agents.

The reason that the Scientific Committee preferred placebo control and a minimum of one year follow-up is based upon the observation that in most studies where placebo therapy has been used, the symptoms and the flow of the placebo arm have shown improvement at least over a short term. This is even taken into account that you can estimate the true placebo effect only after the organization of an initial placebo run-in period prior to the baseline to discount as much as possible the universally known phenomenon of the improvement of symptoms after placebo therapy.

One can regret this lack of scientific purity of not having a placebo arm, of course, but on the other hand there is some rationale in comparing a plant extract, in this case Permixon®, with a recognized pharmaceutical drug, in this case finasteride, whose scientifically demonstrated efficacy is established on its specific 5-α reductase inhibition. It provides at least one recognized parameter in the overall soft data on BPH, which we now call LUTS, standing for lower urinary tract symptoms, since we are not even sure that by measuring the size of the prostate, evaluating the symptoms and the urine flow, we can definitely make the clinical diagnosis of benign prostatic hyperplasia. A further incentive is the fact that two previous trials with an appropriate placebo response versus Permixon®, which were contradictory [2,3], could be matched against four contemporary clinical trials with a placebo effect versus finasteride. Of course, no one could know at the time that this trial was initiated that the outcome of a randomized, placebo controlled clinical trial comparing terasozin and finasteride would show disappointing results for finasteride monotherapy performing only slightly better than placebo [4]. However, a subsequent metanalysis on all finasteride trials concluded that there was a strong positive correlation between prostate volume and clinical response. In this

analysis it could be concluded that finasteride does indeed perform as expected in patients with larger prostates while LUTS with smaller glands showed far fewer positive effects from the therapy [5].

Lastly, we have to consider that the endpoint of the study is focused on the relief of symptoms of men with mild or moderate symptoms of BPH and that the ultimate clinical result would only suggest that this type of medical treatment could be a service to the bothered patient over the watchful waiting.

We personally have more difficulties with the short duration of the study since it has been reported that finasteride shows increasing efficacy after a minimum follow-up of three months and certainly improving up till twelve months after initiation of therapy [6]. It is also recognized that any placebo effect which is certainly present in each arm of every trial on BPH will fade in time [7]. With this background in mind, we can face the reality of the data where 320 mg of Permixon® are compared to 5 mg of PROSCAR, using the International Prostate Symptom Score (I-PSS) as the primary endpoint.

Outcome data were comparable as to the decrease in I-PSS, improved quality of life and increased peak urinary flow rate (Q max). Finasteride showed its recognized efficacy to lower the serum PSA levels (−41%) and the decrease in prostate volume (−18%). These changes were not noted in the Permixon® treatment arm. The question concerning the prostate volume and the specific activity of finasteride on larger volumes is not analyzed in this report.

It is, however, recorded in the intercurrent clinical events that seven patients in the Permixon® arm went into acute urinary retention versus three patients in the PROSCAR arm reflecting the contemporary observation that very few patients with LUTS enter our urological wards with acute retention. It is somewhat surprising to note in Table III that 86 (16%) of the patients withdrew from the Permixon® arm versus 61 (11%) from the PROSCAR arm. From Table VII we confirm the rarity of acute retention as well as decreased libido and impotence in the Permixon® and in the PROSCAR arm respectively being 1.3, 2.2, and 1.5 versus 0.6, 3.0, and 2.8. No statistically significant differences were noted between the two treatment groups for any intercurrent event. These figures contradict somewhat the statement that finasteride provoked a marked deterioration in the sexual function score since there is no evidence that a 9% increase in the symptom score represents a marked deterioration. We suggest that the size of the study shows statistically significant differences which may not be clinically significant. So can we conclude that both treatments relieve the symptoms of BPH in about 2/3 of the patients despite an apparent difference in mechanism of action?

Are we allowed to conclude that the lack of a placebo run-in leaves us with a sizable placebo effect that is difficult to measure? We now know that finasteride's efficacy is rather limited in a short term perspective but that the drug is capable of halting the progression of the disease in the long run, an assumption that cannot be made in the present study. We look forward to the ongoing investigations to clarify the mode of action of *Serenoa repens* agents.

We want to congratulate our colleagues for responding to this challenge and finishing with the rapid accrual of more than a 1,000 men to evaluate the efficacy and toxicity of both Permixon® and PROSCAR in the relief of patients with lower urinary tract symptoms, most of which probably BPH. We hope to see more randomized trials in the near future confirming or refuting the data obtained in this trial. We need more randomized trials in this area of disagreement on many aspects of prostate diseases and ways to remedy them.

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## References

1. Cockett ATK, Khoury S, Aso Y, Chatelain C, Denis L, Griffiths K, Murphy G: Proceedings of the Third International Consultation on Benign Prostatic Hyperplasia (BPH). Paris: SCI, 1996.
2. Boccafoschi C, Annoscia S: Confronto fra estratto di serenoa repens e palcebo mediate prova clinical controllata in pazienti con adenomatosi prostatica. Urologia 50:1257–1268, 1983.
3. Reese Smith H, Memon A, Smart CJ, Dewbury K: The value of permixon in benign prostatic hypertrophy. Br J Urol 58:36–40, 1986.
4. Lepor H: A Department of Veterans Affairs (VA) cooperative randomized, placebo-controlled clinical trial of the safety and efficacy of terazosin and finasteride monotherapy and terazosin/finasteride combination therapy in men with clinical BPH. J Urol 155:587A, 1996.
5. Boyle P, Gould AL: Prostate volume predicts outcome of treatment of BPH with finasteride: Meta-analysis of randomised clinical trials. J Urol 155:572A, 1996.
6. Gormley GJ, Stoner E, Bruskewitz RC, et al: The effect of finasteride in men with benign prostatic hyperplasia. New Engl J Med 327:1185–1191, 1992.
7. Nickel JC and the Canadian PROSPECT Study Group: Placebo therapy in benign prostatic hyperplasia. Can J Urol 3:33A, 1996.