Androgen deprivation therapy prescription, blood and bone-density testing in a French population-based study exploring adherence to the French prostate cancer guidelines

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Short communication

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Abstract (198/200 words)

The safety profile of androgen deprivation therapy (ADT) is well known, and cardiovascular and osteoporosis risk factors should be assessed before ADT initiation.

In order to examine whether the French Committee of Urologic Oncology prostate cancer (PCa) guidelines were properly followed by clinicians, including urologists, oncologists and radiotherapists, we used a nationwide comprehensive cohort of prostate cancer patients, who were new ADT users in 2011 and were followed up to 2013. Reimbursements for biological examinations and prescribers were identified, as well as PCa specialist consultations at drug initiation. Our results in this French cohort showed that the proportions of patients resorting to specialised care between one year and 3 months before ADT initiation and in the 6 months following was around 40 % for fasting glucose and 30 % for lipid assessments. Bone densitometry was performed on around 1% of patients. In the 12 months after ADT initiation, 75% of the patients were seen by a urologist and around 47% by an oncologist or a radiotherapist.

Overall, there is still room for improvement in terms of ADT monitoring by clinicians and in the information provided to general practitioners and patients regarding the expected adverse effects of this treatment.

Short communication

Androgen deprivation therapy (ADT) is a cornerstone therapy in prostate cancer (PCa) treatment. This treatment is associated with several adverse effects such as bone-mineral density decrease and related fractures, insulin resistance with an increased risk of diabetes pseudo-metabolic syndrome, and cardiovascular events[1,2].

Before ADT initiation, the French Committee of Urologic Oncology (CCAFU)[3] recommends a clinical examination of patients to look for cardiovascular and osteoporosis risk factors. In addition to bone-density testing (BDT), biological examinations should include fasting blood glucose, vitamin D test and lipid assessment. During ADT follow-up, in addition to blood glucose, vitamin D and lipid examinations, blood PSA levels should be tested. However, a blood test for testosterone is not recommended as part of the ADT follow-up. The frequency of biological examinations is not clearly defined. The identification of one or several abnormalities following BDT and blood glucose, vitamin and lipid tests should lead to a specialist consultation (cardiologist, rheumatologist…) and, if necessary, to the introduction of specific treatments with a change in life-style factors.

In a 6-month cross-sectional French study using questionnaires administered to clinicians between 2012 and 2013 concerning the care and monitoring of 1100 patients treated with luteinizing hormone-releasing hormone (LHRH) agonist, Hennequin et al. reported that fasting blood glucose tests were prescribed to 41%, lipid assessments to 36%, BDT to 11 %, electrocardiograms to 25 %, and total blood testosterone levels to 5%[4].

In order to examine whether the French CCAFU prostate guidelines (issued at the time of the study[5]) were correctly followed by clinicians, including urologists, oncologists and radiotherapists, we used a nationwide cohort of French PCa patients, who were new users of ADT in 2011 and were followed up to 2013[6]. Using the French "SNIIRAM" database, a comprehensive and representative claims database[7], PCa diagnosis over the study period was based on the International Classification Disease 10th edition codes 'C61' or 'D40.0' for hospitalisation or on qualification for long-term disease status which provides 100% reimbursement of all disease-related claims. Biological examination

reimbursements and prescribers were identified, as well as PCa specialist consultations before and after drug initiation (one year to 3 months before, and in the 6 months following). These reimbursements provide proof that the procedures have been carried out. Prescriptions that are not followed by the procedure do not result in reimbursement.

In 2011, 23 407 new ADT users were identified (median age, 75 years): 67 % were treated with LRHR agonist, 17 % with combined androgen blockade, 12 % with anti-androgen, and 4 % with LHRH antagonist. The most common baseline comorbidities included hypertension (66.5%), the use of lipid-lowering drugs (44.6%), and the use of anti-platelets (31.9%) and anti-diabetics (16.7%). In the 6 months before ADT initiation, 83% of patients had consulted a urologist and 25% an oncologist or a radiotherapist. In the 12 months after ADT initiation, 75% of patients saw a urologist and around 47% an oncologist or radiotherapist.

Figure 1 shows the proportions of patients undergoing specific procedures, blood examinations and BDT in the 3 months to one year before ADT initiation and in the 6 months following.

While the examination of blood testosterone levels is only required to confirm CRPC[3], testosterone level monitoring during androgen deprivation can be useful at earlier stages. Indeed, testosterone levels < 50 ng/dL under androgen deprivation confirm the success of the treatment administered and patient compliance. Nadir and spikes of blood testosterone have also been reported as strong prognosticators[8]. However, in our study, blood testosterone testing was only performed on fewer than 15% of patients after initiation of ADT.

Vitamin D, fasting blood glucose and lipid tests were mainly prescribed by general practitioners (GP) in the 3 months before and 6 months after ADT initiation (Figure 2). Regarding PSA in the 3 months before ADT initiation, we observed that tests were prescribed by urologists, other specialists and GPs in respectively 31.3%, 5.7% and 37.6% of the cases. Blood PSA and testosterone level assessments in the 6 months after ADT initiation were mainly prescribed by urologists (36.4%).

Although these tests are recommended by CCAFU, our results showed that, at the time of ADT initiation, blood examinations and BDT were not performed on all patients. One limitation was the

use of the French "SNIIRAM" database, a healthcare reimbursement database[7]. This database reflects the actual completion of prescribed examinations. However, the reason why some examinations were not performed remains unclear and could relate to failure to prescribe on the part of clinicians, and also to patient non-compliance. We also recognize that patients who died early or those with a short follow-up period may not have had time to undergo their examinations.

Regarding the prescriber specialty, the investigation of CV and fracture risk factors via vitamin D, fasting blood glucose and lipid tests was mainly initiated by GPs whereas blood PSA and testosterone level assessment seemed more likely to be prescribed by specialists.

The results of the study by Hennequin et al. using questionnaires[4] are consistent with those from our study, except for BDT: 11% of clinicians in their study reported having prescribed BDT whereas 1 % of the patients or less in our study actually underwent this assessment in the year before or in the six months after ADT initiation. This percentage is well below that in an American study showing that 15 to 20 % of patients underwent BDT within the 3-year period surrounding ADT initiation, which still appeared below the ideal testing rate[9].

In a review commentary on ADT cardio-metabolic toxicity, Khouri and Harrisson considered that the variety of backgrounds of the physicians who administer ADT predisposed to a heterogeneous approach to screening or monitoring[10]. Our results suggest that the implementation of blood tests and BDT by urologists, radiotherapists and oncologists remains sub-optimal whatever the specialty they belong to. In a review on ADT adverse effects, Rhee et al. discussed Australian practice[1]. They indicated that the management of long-term adverse events under ADT should include a pro-active attitude to prevent reduce or address them. Thus, in addition to the educational package (provided in their review), a 'Men's Health Clinic' has been established in Austin, where a multidisciplinary team is responsible for monitoring and managing all patients who initiate ADT.

Overall, there is still room for improvement in terms of ADT monitoring by clinicians and in terms of information provided to GPs and patients regarding the expected adverse effects of this treatment.

The development of educational programs for patients and caregivers could be discussed, to improve the overall detection and management of ADT adverse events.

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Figure 1. Prevalence of patients with specific care, blood examinations and bone-density testing (at least one reimbursement per considered variable) before and after ADT initiation.

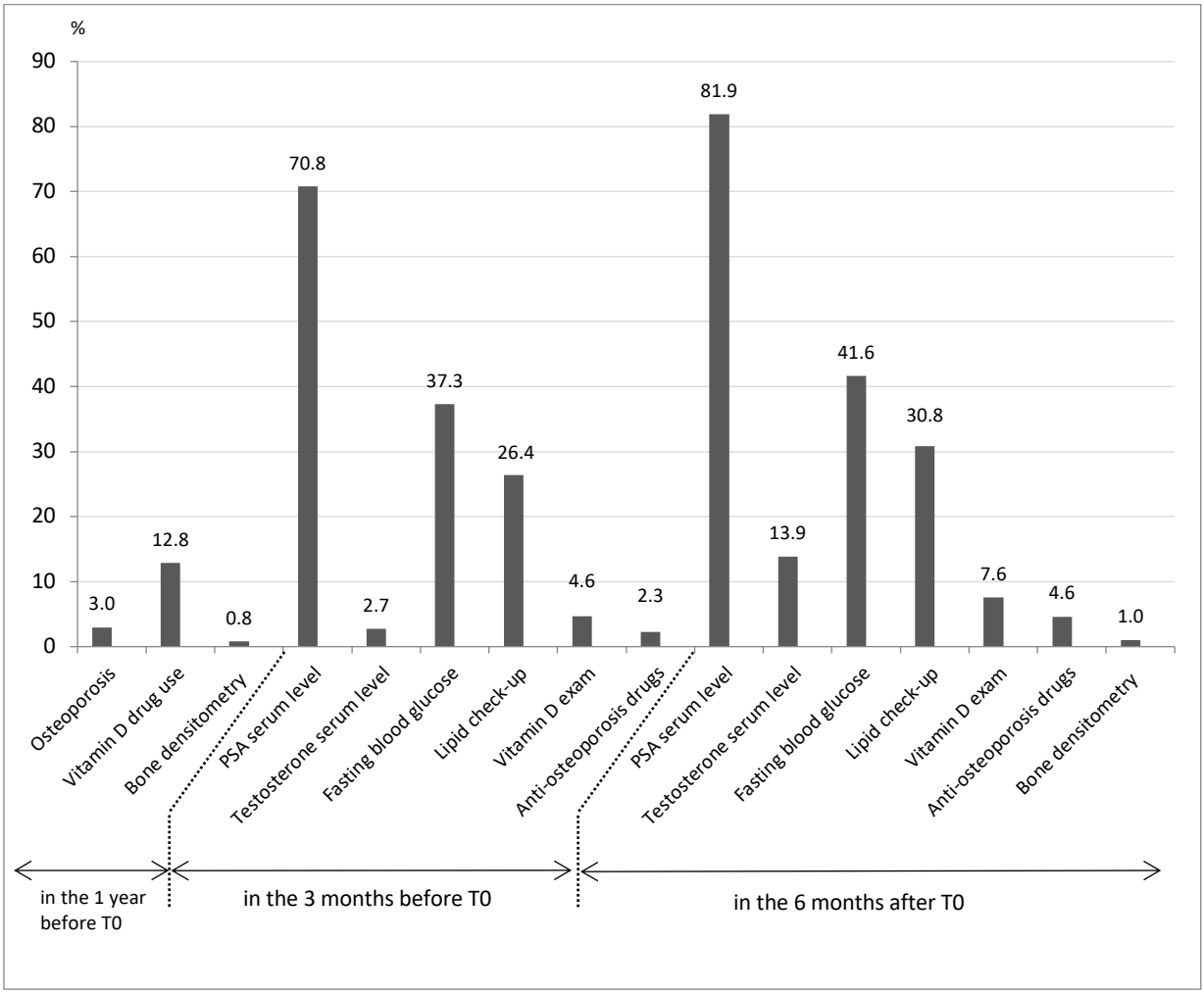

Figure 2. Prevalence of prescribed blood examination by specialty, before and after ADT initiation.

* Blood examinations prescribed by general practitioners only. Urologists and oncologists / radiotherapists are un-mutually exclusive categories.