Quality of Life Improvement in Patients Treated with Degarelix versus Leuprorelin for Advanced Prostate Cancer

Dawn Lee,*,† Sandy Kildegaard Nielsen,† Marjolijn van Keep,† Fredrik Andersson‡ and Damien Greene§

From the BresMed (DL, SKN), Sheffield and Sunderland Royal Hospital (DG), Sunderland, United Kingdom, BresMed (MvK), Utrecht, The Netherlands, Ferring International PharmaScience Center (FA), Copenhagen, Denmark, and Center for Medical Technology Assessment (FA), Linköping University, Linköping, Sweden

Purpose: We used responses to questionnaires included in the CS21 degarelix trial and published mapping algorithms to address the paucity of evidence for health related quality of life in patients with advanced hormone dependent prostate cancer treated with degarelix.

Materials and Methods: We measured health related quality of life in 610 patients enrolled in the CS21 trial using SF-12® and EORTC QLQ-C30. Based on responses to these questionnaires we estimated patient utility using 4 published mapping algorithms. Utility was tested for relationships with aspects of the symptom and side effect burden that may be affected by degarelix treatment, that is prostate specific antigen progression and adverse events.

Results: Average utility in patients without prostate specific antigen progression or an adverse event was 0.742, similar to previously published utilities for nonprogressed prostate cancer states. Prostate specific antigen progression was associated with a utility decrement of between 0.062 and 0.134 depending on the mapping algorithm used. Of adverse events considered in our analysis musculoskeletal events were associated with the greatest effects on patient utility with a decrement of between 0.029 and 0.086. The 4 mapping algorithms generated similar utility estimates, although values derived from SF-12 were consistently lower than those derived from EORTC QLQ-C30.

Conclusions: Prostate specific antigen progression status and the incidence of treatment and disease related adverse events result in significant decrements to patient health related quality of life. By slowing prostate specific antigen progression degarelix may improve patient utility and the health related quality of life burden.

Key Words: prostatic neoplasms, drug therapy, quality of life, cost-benefit analysis, questionnaires

Abbreviations and Acronyms

8D = 8 Dimensions

EORTC = European Organisation for Research and Treatment of Cancer

EQ-5D = EuroQol-5 Dimensions

HRQL = health related quality of life

LHRH = luteinizing hormone-releasing hormone

PFS = progression-free survival

PSA = prostate specific antigen

QLQ-C30 = Quality of Life Questionnaire-C30

UK = United Kingdom

Accepted for publication September 19, 2014.

Study received institutional review board approval.

Supported by Ferring Pharmaceuticals A/S.

* Correspondence: BresMed, North Church House, 84 Queen St., Sheffield, S1 2DW, United Kingdom (telephone: +44 (0)114 309 4372; FAX: +44 (0)114 270 0422; e-mail: dlee@bresmed.co.uk).

† Financial interest and/or other relationship with BresMed and Ferring.

‡ Financial interest and/or other relationship with Ferring Pharmaceuticals.

§ Financial interest and/or other relationship with the National Health Service.

For another article on a related topic see page 1023.

Locally advanced and metastatic prostate cancer is commonly associated with a considerable symptom and treatment related burden in patients with substantial implications for quality of life.[1] Available evidence indicates that HRQL decreases as patients progress to later lines of treatment.[1–5] This is attributable to disease progression, anxiety and distress about PSA levels and the side effects of current hormonal treatments, which can adversely affect patient daily function as well as the sense of well-being.

0022-5347/15/1933-0839/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.09.098
Vol. 193, 839-846, March 2015
Printed in U.S.A.

Most men with advanced prostate cancer are treated with LHRH agonists such as leuprorelin, goserelin or triptorelin. Although the aim of these treatments is to reduce testosterone to castrate levels, LHRH agonists are typically associated with an initial surge in testosterone known as a testosterone flare. This delays castration and can result in clinical symptoms affecting patient quality of life. Potential flare effects include increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression and fatal cardiovascular events due to hypercoagulation status.[6,7] Therefore, LHRH agonists are often first prescribed in combination with antiandrogen therapy such as bicalutamide to reduce flare.[6] However, this has not proved to decrease the incidence of testosterone flare side effects.[7]

Degarelix is not associated with testosterone flare and it represents an alternative to treatment with LHRH agonists in patients with advanced hormone dependent prostate cancer.[8,9] Although it acts on the same receptor (gonadotropin-releasing hormone receptor) as LHRH agonists, degarelix is a receptor antagonist that blocks the receptor to achieve an immediate, sustained reduction in testosterone. The rapid effect avoids the initial testosterone surges that characterize treatment with LHRH agonists.[8] Klotz et al found that degarelix significantly improved PSA PFS relative to LHRH agonists.[9] Although the mechanism of action by which PSA PFS is improved is not fully established, it is likely due to short-term and long-term testosterone suppression.

To our knowledge utility estimates in patients treated with degarelix have not been published previously. However, HRQL measures are required to assess the cost-effectiveness of treatment by cost utility analysis, which is used to inform reimbursement decisions. Utilities represent a valuation of HRQL on a continuum of 0 to 1, where 0 is equivalent to death and 1 represents the best possible health state.[10]

When utilities cannot be directly derived from HRQL instruments collected in a clinical trial such as EQ-5D, an algorithm can often be used to derive such utilities from other HRQL questionnaires. This is known as mapping. Mapping algorithms use available data from questionnaire responses to produce preference based, generic utility estimates.

The CS21 trial included 2 measurements of patient HRQL, that is SF-12, version 2 and the EORTC QLQ-C30.[11] Preference based utility estimates can be derived from patient responses to these instruments using mapping techniques. In this study we used various published mapping algorithms to estimate patient utility from CS21 trial observations. Using these estimates we examined the effect of PSA progression as well as key disease and treatment related clinical adverse events on patient utility. In addition, we examined the beneficial effect of degarelix on HRQL in patients with advanced prostate cancer.

METHODS

Study Population

The CS21 trial recorded HRQL data on 610 patients 18 years old or older with histologically confirmed adenocarcinoma of the prostate in whom endocrine treatment was indicated (except for neoadjuvant hormonal therapy).[11] Disease stage was defined as localized (T1/2, NX or N0 and M0), locally advanced (T3/4, NX or N0 and M0 or N1 and M), metastatic or not classifiable (increasing PSA after radical prostatectomy or radiotherapy). Antiandrogen flare protection was administered in 4 (6.3%), 6 (11.5%), 9 (19.1%) and 3 patients (7.7%), respectively.

Table 1 lists baseline patient characteristics. Patients received degarelix at a starting dose of 240 mg followed by 12 monthly (every 28 days) maintenance doses of 80 or 160 mg (240/80 mg and 240/160 mg, respectively) or 12 monthly (every 28 days) doses of leuprorelin 7.5 mg. The degarelix 240/160 mg group was not included in this analysis of the treatment effect because this is not the licensed dosing regimen.[11]

HRQL Measures

The SF-12 and EORTC QLQ-C30 questionnaires were administered at days 0 (baseline), 28, 84 and 168, and at the end of study visit to measure generic and cancer specific quality of life. SF-12, a 12-item generic measure of HRQL, is an abbreviated version of the SF-36® questionnaire.[12] EORTC QLQ-C30 is a cancer specific questionnaire consisting of 30 questions that is frequently used to assess quality of life in patients in various disease states. Responses are transformed to scores on a set of 5

Table 1. *Baseline patient characteristics*[11]

	Degarelix 240/80 mg		Leuprorelin 7.5 mg/mo	
No. intent to treat pts	207		201	
Median age (range)	72	(51–89)	74	(52–98)
Median ng/ml testosterone (25th–75th percentile)	4.11 (3.05–5.32)		3.84 (2.91–5.01)	
Median ng/ml PSA (25th–75th percentile)	19.8	(9.4–46)	17.4	(8.4–56)
No. disease stage (%):				
Localised	69	(33)	63	(31)
Locally advanced	64	(31)	52	(26)
Metastatic	37	(18)	47	(23)
Not classifiable	37	(18)	39	(19)
No. Gleason score (%):				
2–4	20	(10)	24	(12)
5–6	68	(33)	63	(32)
7	63	(30)	62	(31)
8–10	56	(27)	51	(26)
No. PSA ng/ml subgroup (%):				
Less than 10	55	(27)	64	(32)
10–20	52	(25)	44	(22)
Greater than 20	52	(26)	38	(19)
Greater than 50	48	(23)	55	(27)