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AROMATASE Inhibitors for the Treatment of Male Hypogonadism

Scientific Rationale

Many men of reproductive age are overweight or obese, with obesity being clearly linked to impaired testicular function (low serum testosterone, reduced sperm concentration and increased sperm DNA damage). Obesity is associated with an increase in serum estradiol levels, principally caused by the conversion of testosterone into estrogen by adipose tissue aromatase action. Rising estrogen levels then impair sperm production by:

- Estrogen negatively feeds back on the H-P axis reducing gonadotrophin drive for the production of testosterone, leading to a further reduction in testosterone levels and impaired spermatogenesis.
- Estrogen has a direct negative impact on spermatogenesis. The use of aromatase enzyme inhibitors such as letrozole or anastrazole has been shown to block this conversion of testosterone to estrogen and boost testicular endocrine function plus spermatogenesis (1-4).

Indication for use of AI:

- Obese men with confirmed low serum testosterone (< 11 nmol with symptoms of androgen deficiency or any man with levels < 8 nmol) on an early morning sample. And Either:
- Azoospermia. Several studies have shown a return of sperm to the ejaculate, or on repeat testicular biopsy, in up to a quarter of previously azoospermic men following at least 3-6 months of AI therapy (1, 2). AI have also been shown to improve chances of obtaining sperm on microTESE in XXY men.
- Severe oligospermia reducing the probability of obtaining sufficient high quality sperm for IVF-ICSI.
- Severe OAT and a reluctance to undergo IVF-ICSI (i.e. patient desire for IUI or attempted natural conception).
- Short term management of androgen deficiency symptoms while undergoing infertility treatment. AI will often produce a 2-3 fold increase in serum testosterone (1-4) and a resolution of androgen deficiency symptoms plus a significant weight loss (result of a testosterone mediated increased in muscle mass and exercise tolerance).

Medication Regime:

Both letrozole (2.5 mg tablets) and anastrazole (1 mg tablets) are available on the PBS. While letrozole is a more potent AI compared to anastrazole, head-to-head comparisons have not shown any clear advantage of one AI over the other in terms of normalisation of testosterone levels and spermatogenesis (3,4). Starting dose is one tablet of either letrozole (2.5 mg/week) or anastrazole (1 mg/day) per day and then review in 2-3 weeks following repeat checking of serum testosterone. Aim for a serum testosterone level around 15-20 nmol, but not exceeding 30 nmol as this may produce polycythaemia and increased thrombotic risk. Many men require a maintenance dose of only 2.5 mg letrozole every 7-10 days to maintain a high normal range of testosterone. AI have been noted to on rare occasions to alter liver function so it is suggested to repeat testosterone and LFTs within 6 weeks of starting the medication. Side effects are uncommon but include fatigue, nausea,

dizziness, joint/muscle aches and headache (3). Paradoxically, despite improving testosterone levels AI may impair libido due to excessive suppression of estrogen. In the event a patient experiences these side effects either decrease the dose of letrozole or move to the weaker AI anastrazole. Long term suppression of estrogen production by AI may increase the risk of osteoporosis (3). Therefore it is not advisable to use an AI for longer than 12 months without checking bone density, and such prolonged “off label” treatment is probably outside the aims of reproductive medicine. However, clinical experience suggests that many obese men will lose considerable amounts of weight quickly on AI therapy, naturally reducing their estradiol levels and possible need for AI treatment in the medium term.

REFERENCES:

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The above information can be found in “Reproductive health management clinical guidelines” document, on the Repromed intranet. Please refer to the full document.