Physiological dose reverse rhythm testosterone treatment abolishes the development of permanent gynaecomastia in adolescent boys with 47,XXY Klinefelter syndrome (KS)

Gary Butler, UCL Hospital & UCL Institute of Child Health

Gynaecomastia as a feature of KS
- Reports of incidence 40-60% (30-40% non-KS boys)
- Different natural history from non-KS as usually do not resolve spontaneously
- Persistent due to low testosterone/obesity/increased aromatase activity
- Major psychological morbidity

Reasons to treat KS boys with testosterone

Biochemical hypogonadism
Low testosterone: often not before puberty stage G4

Clinical hypogonadism
Slow virilisation including micropenis
Poor muscle development/tone
High BMI
Gynaecomastia?: but when to start?

Patients: from UCLH Klinefelter syndrome clinic
Local and national referrals
Currently over 50 patients; 29 over 11 yr at time of study

Methods
Prospective evaluation of gynaecomastia in 29 boys over 11yr
Recording of Tanner puberty stage & breast stage
Measurement of breast disc diameter by palpation

Started routine physiological testosterone replacement schedule but in reverse rhythm je taken in morning using testosterone undecanoate (oral) 40mg od or Tostran (transdermal) 20mg od but NOT SUSTANON im due to adverse pharmacokinetics

Results
8/29 developed gynaecomastia. Only one had a high BMI
All offered physiological testosterone replacement
2 failed to comply: gynaecomastia did not resolve
3 testosterone undecanoate TU (Restandol) 40mg om
3 transdermal testosterone (Tostran) 20mg om

<table>
<thead>
<tr>
<th>Age onset (yr)</th>
<th>G stage</th>
<th>TV (ml)</th>
<th>B stage</th>
<th>Disc (cm)</th>
<th>BMI SDS</th>
<th>Age offset (yr)</th>
<th>Time (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.9</td>
<td>2-4</td>
<td>3-6</td>
<td>2-3</td>
<td>2.1</td>
<td>0.6</td>
<td>13.6</td>
<td>0.8</td>
</tr>
<tr>
<td>11.4-14.2</td>
<td></td>
<td>1-3</td>
<td></td>
<td></td>
<td>-1.33 to +3.0</td>
<td>12.5-15.9</td>
<td>0.2-1.7</td>
</tr>
</tbody>
</table>

Conclusions
Reverse rhythm testosterone, using a morning administration regimen started at the onset of gynaecomastia and then given continuously in physiological dose increments, abolishes the development of permanent gynaecomastia in adolescent boys with KS