PostScript

MATTERS ARISING

Probable adverse effects of long term use of somatostatin analogues in patients with RA

We would like to comment on two pilot studies recently published in the *Annals of the Rheumatic Diseases* by Paran *et al* and Koseoglu and Koseoglu about the effects of octreotide, a somatostatin (SOM) analogue, in patients with refractory rheumatoid arthritis (RA).^{1,2} Both groups reported minor adverse effects as shown by routine clinical and laboratory assessment. However, because these SOM analogues had some positive effects on disease activity in these difficult patients, they concluded that they might be used as disease modifying antirheumatic drugs (DMARDs) and that larger randomised controlled clinical trials were warranted.

Although we welcome research on new DMARDs, in this instance we feel obliged to point out some probable adverse effects of the long term use of SOM analogues in patients with RA that were not considered in these preliminary trials.

As reviewed by Paran *et al*, SOM has some immunomodulatory and analgesic effects and these constitute the rationale for the use of SOM analogues in the treatment of RA. However, the main function of SOM is to regulate the production of growth hormone (GH) by inhibiting pituitary GH production in response to GH releasing hormone. Consequently, systemic administration of SOM or its analogues causes GH deficiency.³

Although most of us recognise the consequences of GH deficiency in children (for example, dwarfism), its effects in adults are not as widely recognised. Studies on subjects with adult onset GH deficiency disclosed a complex syndrome that includes⁴:

- Alterations in metabolism and body composition (excessive and centrally distributed body fat, osteopenia, and generalised muscle atrophy—that is, sarcopenia)
- Decreased muscle strength and exercise capacity
- Increased cardiovascular mortality
- Reduced psychological wellbeing and quality of life.

These adverse effects are ameliorated by treatment with exogenous GH, clearly demonstrating that GH has an important role in adult life.⁴

These possible adverse effects of the long term use of SOM analogues are particularly relevant in patients with RA who already present with an impaired GH/insulin-like growth factor I axis,^{5,6} sarcopenia, low bone mineral density, abdominal obesity,⁷ poor physical fitness,⁸ reduced quality of life,⁹ and high cardiovascular mortality.¹⁰

For these reasons, we suggest that if and when large, randomised controlled clinical trials of SOM analogues are conducted in patients with RA, they should include not only routine clinical and laboratory assessment, but also measures of body composition, physical fitness, psychological wellbeing, and cardiovascular health. This

would be the only way to detect these serious adverse effects that might outweigh the benefits of SOM analogues in the treatment of RA.

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Authors' reply

Marcora *et al* raise an important point about the potential effect of somatostatin on the growth hormone axis and its ability to induce growth hormone deficiency. Indeed, Calabresi *et al* have shown that intravenous somatostatin may decrease the mass and frequency of growth hormone secretory bursts in healthy volunteers, but this study is of short term treatment and uses the native somatostatin and not an analogue.¹ The native hormone binds all five somatostatin receptors, which may lead to significantly more side effects than the receptor subtype specific

somatostatin analogues.^{2,3} The potential of somatostatin to induce growth hormone deficiency obviously cannot be evaluated in patients with acromegaly. However, long term studies of somatostatin analogues in the treatment of endocrine tumours of the gastrointestinal tract have shown that they are safe, and that the most important adverse event is the development of gallstones.⁴ In these studies, growth hormone deficiency was not a matter of great concern.

We agree that future studies of somatostatin in patients with rheumatoid arthritis should include an appropriate evaluation of its hormonal effects. These future studies should also assess the optimal somatostatin analogue and the best dosage to use for both efficacy and safety.

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