# Debate & Analysis

# The increasing demand for knee replacements:

## a hostage to fortune

### THE GROWING PROBLEM

Osteoarthritis (OA) of the knee is a huge problem. Even in our small group practice we have hundreds of patients who suffer daily pain and disability. Knee replacement surgery is a very effective remedy, but can be risky, and quite a lot of patients are medically unfit for the procedure. Analgesics, systemic and topical non-steroidal anti-inflammatory drugs, and intra-articular (IA) steroid injections provide limited or short-term benefits and physiotherapy and other conservative approaches may improve mobility but have less impact on pain.

Things are going to get worse in the future. Knee pain and disability are very strongly related to obesity, which, as we know, is rising fast. We are putting in knee replacements much more frequently than even 5 years ago. According to the National Joint Registry there were over 80 000 primary procedures in 2011; up from around 60 000 5 years before, and increasing by around 3% annually. Around 17% of procedures are done in patients aged <60 years, and the average age is 67 years. The majority of patients are obese and this proportion is growing. In 2013, 21% of patients had a BMI of ≥35, whereas in 2006 it was 15%.[1] Younger, and therefore more active patients, are at greater risk of implant failure, as are obese patients. There are around 5000 (6%) revisions out of 88 000 total procedures in England each year. However the need for revisions is bound to increase considerably with the increase in primary procedures and the tendency to operate on younger and more obese patients. In the US in 2010 there were 55 000 revisions (8%) compared with 658 000 primary procedures.[2] Nearly half of the revisions were in patients <65 years, emphasising the increased risk of failure in younger patients. The need for revision could increase five times by 2030. Of the knee prostheses in place in patients now in the US, about 1 million are likely to need revision surgery during the expected lifetimes of the patients.[3] I have failed to find the equivalent projections for the UK and oddly, the recent National Institute for Health and Care Excellence (NICE) guidelines on OA makes no mention of this.[4]

So, is there any evidence-based way in which we can help with pain and disability and reduce the burden and the morbidity inherent in the knee replacement approach? In particular, can we delay knee replacement in a cost-effective manner, while maintaining function and fitness for work, and can we help patients who are unfit for major surgery? There may be, and it is strange that so few doctors in the UK are using this approach.

### A PARTIAL SOLUTION?

Hyaluronans are a group of large polysaccharide (glycosaminoglycan) molecules, which are a major component of synovial fluid. They make it viscous, and they also seem to have a role in increasing the water content of the cartilage and increasing its resilience. Degenerative joints contain fewer of these chemicals than healthy joints, and this appears to make the joint more prone to further damage to the articular cartilage cells.[5] Experimentally, injections of hyaluronans can reduce the progression of degenerative change in rats that have had their anterior cruciate ligaments divided.[6] The medical application of these chemicals started off as an artificial fluid for eye surgery in the 1970s, and these treatments have been used on millions of patients. Then, as with many medical advances, it was spotted as a possible treatment for OA by vets, who inject it into horse joints with good results. It then transferred to human medicine, and has been used extensively, especially in Europe. Originally, courses of three to five injections were used, but it is now more commonly given as a single injection.

There are many different products, produced from a variety of sources, most commonly rooster combs, but they are also produced by bacterial fermentation. Some of the makers of these products modify them to increase chemical cross-link bonding in order to enhance the viscosity and reduce the rate at which they are removed from joints. Analysis of synovial fluid 3 months after injecting hylan G-F 20 (Synvisc®) has shown an increase in viscosity as well as in hyaluronic acid (HA) concentration.[7]

### WHAT IS THE EVIDENCE BASE FOR THESE TREATMENTS?

Are they effective, and are they safe? The latter is the easier question to answer. The Cochrane Collaboration systematic review in 2006 pronounced them to be safe.[8] The risks are of an allergic reaction which can affect up to 1% of patients and can require steroid treatment, and the rare complication of intra-articular infection. As far as effectiveness is concerned, the evidence is good overall, but there is a lot of heterogeneity in the research reports. This is not surprising as the individual products vary and the methods of assessment vary even more. Most trials have shown significant benefits over placebo, and also over steroid injections, often with very low *P*-values (<0.001). Interpretation of the trials can be difficult. For example, in a recently published trial of NASHA™ (biotech hyaluronan) of average molecular size, 30.6% of patients responded, which was defined as an improvement in WOMAC pain score of <40% with a minimum change of 5 points. However, so did 26% of placebo patients injected with saline, and the difference was not statistically significant. This is in marked contrast to a very significant difference in the results of a subgroup analysis of patients without a clinical effusion, which showed a response rate of 40.6% versus 19.7% for placebo, *P* = 0.0084. The assessment was carried out at 6 weeks, much earlier than in many studies, and earlier than many patients report maximum benefit.[9] The Cochrane collaboration verdict was:

*'No major safety issues were detected. Overall the aforementioned analyses support the use of the IA class of products in the treatment of knee OA.'*

> "[Hyaluronan] *treatment may actually be modifying the disease, as the animal experiments suggest it might, rather than just providing relief of symptoms.*"

*"However,* [NICE] *did not consider the potential benefit in terms of delay in the need for surgery, and they included no recent cost-effectiveness studies in their analysis."*

A recent meta-analysis of trials versus saline controls restricted to US licensed products (published in September 2013 and not referenced in the NICE guidelines)[4] reached similar conclusions. *P*-values for benefits on pain and function were <0.001. While advising caution because of the heterogeneity of the results, and variable trial quality, they concluded that these treatments are safe and effective.[10] The AMELIA trial, using repeated treatments for >3 years, found that the number of responders increased with repeated injections, which suggests that the treatment may actually be modifying the disease, as the animal experiments suggest it might, rather than just providing relief of symptoms.[11]

## EFFECTIVE BUT COST-EFFECTIVE?

NICE first looked at the issue in 2008 and concluded:

'*Overall, the evidence suggests that hyaluronans and hylan derivatives seem to be superior to placebo in terms of efficacy and quality of life outcomes in patients with OA of the knee ...*' [12]

The recently updated NICE guidance[4] is more vague on the issue of effectiveness, accepting that many studies show an effect, but they are critical of the quality of many studies. Their conclusion '*Do not offer intra-articular hyaluronan injections for the management of osteoarthritis*' is mainly based on an assessment that they are 'unlikely' to be cost effective, due to the effect sizes found in the various studies, and the known costs of the treatments. However, they did not consider the potential benefit in terms of delay in the need for surgery, and they included no recent cost-effectiveness studies in their analysis. This is odd, since a Canadian cost-effectiveness study comparing hyaluronan with usual care estimated the benefit as costing CAN $10 000 per quality-adjusted life year, well within the NICE threshold.[13] NICE discounted this study because of the lack of a placebo group, which seems harsh for a pragmatic study.

One retrospective analysis of patients with severe OA who were eligible for surgery compared treated patients with other patients who were not suitable for injections and 75% of the treated patients were able to delay surgery for >3 years.[14]

What does hyaluronan treatment cost? For a typical patient who has a course every 9 months of one of the more expensive cross-linked hylan G-F 20 products it is about £22 per month per knee, which is similar to, or less than, the cost of many drugs of modest benefit. It has to be given by a trained professional but it only takes 5 minutes or so. Perhaps it is time that we looked ahead a bit and considered how we should deal with the probable huge increase in the need for knee surgery, and actively explored alternative ways of dealing with it, one of which might be hyaluronan injections.

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