Is chondroitin sulfate plus glucosamine superior to placebo in the treatment of knee osteoarthritis?

We read with interest the article by Hochberg *et al*[1] related to the efficacy and safety of chondroitin sulfate plus glucosamine hydrochloride (CS+GH) versus celecoxib in patients with knee osteoarthritis and severe pain. The study suggested that CS +GH has comparable efficacy to celecoxib in reducing pain, stiffness, functional limitation and joint swelling/effusion after 6 months with a good safety profile. These results were 'promising'. We really appreciate the work that was done by the authors. However, there are worthwhile issues that need to be explored.

The study was designed as a non-inferiority trial without placebo arm. The authors explained that, 'The use of a placebo group was not considered appropriate for ethical and methodological reasons'. We agree with this. The authors added that the use of placebo arm was not considered necessary as the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) already compared both active treatments (CS+GH and celecoxib) with placebo and came to a conclusion that a subset of participants with more severe baseline pain appeared to benefit by use of CS+GH as compared with placebo.[2] However, a subsequent GAIT report clearly pointed out that none of the interactions between severe pain and treatment groups were statistically significant over a follow-up of 24 months.[3] In addition, the authors did not mention the Long-term Evaluation of Glucosamine Sulfate (LEGS) study that was published in January 2014.[4] The LEGS study reported that although the glucosamine–chondroitin combination demonstrated reduced knee pain over the study period, it did not show significant symptomatic benefit above placebo. Furthermore, the authors also indicated that the results of their study were in accordance with data from three other studies,[2 5 6] including the original GAIT for the combination. However, it should be noted that the combination group in two of the three studies contained the CS +GH and the manganese ascorbate.[5 6] The therapeutic efficacy of the combination could probably be improved by the manganese ascorbate. Thus, the efficacy of CS+GH versus placebo in the treatment of knee osteoarthritis is still unclear. In such cases, we are not sure whether it is appropriate to conduct a non-inferiority trial without placebo control to examine the efficacy of CS+GH and celecoxib for painful knee osteoarthritis.

The use of placebo control is a standard group in a large number of clinical trials. In consideration of the effects from active treatment that do not depend entirely upon itself, the objective of the placebo control is to account for the placebo effect. Because of the heavily negative connotations of the very words 'placebo effect', Benson *et al*[7] even suggested that the term should be replaced by 'remembered wellness' which should not be belittled or ridiculed. Another systematic review of 130 trials also reported that the placebo has possible small benefits in studies with continuous subjective outcomes and for the treatment of pain.[8]

Above all, without a placebo group to compare against, it is a little hard to know whether the active treatments (CS+GH and celecoxib) themselves had any effect. We respect the great contributions of the authors and we are very much looking forward to the follow-up results of this study.

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