Negrin LL, Vecsei V. Do meta-analyses reveal time-dependent differences between the clinical outcomes achieved by microfracture and autologous chondrocyte implantation in the treatment of cartilage defects of the knee? J Orthop Sci 2013;18(6):940-8.

Design: meta-analysis of randomized trials

Purpose of study: to compare the outcomes of microfracture (MF) vs. autologous chondrocyte implantation (ACI) in the treatment of chondral defects of the knee over comparable followup periods of one, two, and five years

Reasons not to cite as evidence:

- There are significant problems with the included studies which are the basis for the authors' inferences about the effectiveness of ACI versus MF, two of which are at risk of selective outcome reporting based on their protocols at clinicaltrials.gov
    - Crawford 2012 compared the ACI product with the trade name of NeoCart to MF, but listed a primary outcome "the safety and preliminary efficacy of NeoCart" compared to conventional MF
        - This is not a specific outcome, and should be viewed with considerable skepticism, as it is possible to report several outcomes, such as the International Knee Documentation Committee (IKDC), the Knee Injury and Osteoarthritis Outcome Score (KOOS), each with several subscales, as well as a comparison of "responders" which could be defined after the outcome data had become available
    - Vanlauwe 2011 compared an ACI system with M, with primary outcomes of both histological outcomes on biopsy and changes from baseline in the oferall KOOS at 12-18 months
        - These outcomes are, in contrast to those of Crawford 2012, adequately specified
        - In Figure 1, it appears that the KOOS scores were not significantly different between the groups at the 12 to 18 month measurements, and that the ACI group was better than the MCI group at only the 36 month followup, and the effect size is not very large (the interpretation of Figure 1 is complicated by the lack of numerical labeling of the y axis; the lines probably represent 5 points of KOOS, which is the scale used in Figure 2 just below Figure 1)
        - There were differences in favor of ACI in a subgroup defined by treatment greater than or less than 3 years after onset, where ACI is better than MF when the intervention is done less than 3 years after onset
        - Because this subgroup analysis was not in the protocol, it should be seen as exploratory in nature and not as confirmatory

- The authors report in Figures 5 through 7 that ACI is superior to MF in the more recent studies after 2007, and that the superiority declines over the course of time between year 1 and year 5
    - The derivation of the values in these three forest plot figures appears to have been done using formulas which were referenced in a book written in German, and it is not clear how they were derived
    - However, it appears that Figures 2 through 7 compute effect sizes in terms of standard mean differences (SMD) between MCI and MF
    - Table 3 and Figure 2 should go together as representing one-year followup results for MF versus ACI
    - If this is so, then the SMD for Crawford 2012 of 3.62 should mean that the difference in outcome scores, divided by the pooled standard deviation of the outcome scores, should be 3.62
    - This is problematic, because the pre-post difference for Crawford's ACI group was 30 points with a standard deviation (SD) of 15, and for the MF group, the pre-post difference was 13 with a SD of 9
    - The difference in these outcome scores is 30-13=17
    - Since there were 21 MCI patients and 9 MF patients, the pooled SD for the difference scores is 13.6, and the SMD would be 17/13.6=1.25, which is a fairly large effect size but much less than the 3.62 displayed in Figure 2
    - If only the postoperative one year scores, rather than the "difference scores" are compared, then the postop score for the ACI group was 74 and for MF it was 65, with SD of 14 and 11, respectively
    - This would yield a score difference of 74-65=9 and a pooled SD of 13.2 for an SMD of 0.68
- Because the method for computing the SMD and its trend over time is not transparent, this conclusion should not be cited as evidence

Reasons to cite as information:

- The forest plots in Figures 2 through 5 are valuable in showing that the study of a first generation ACI (Knutsen 2007) favored MF over ACI, while the studies of later generation ACI from 2010 to 2012 favor ACI over MF
    - This resolves most of the heterogeneity in effect seen when early and later studies are combined together
- This suggests that there are differences in effectiveness between more recently engineered applications of ACI compared to the 2007 study where the implant was covered with a periosteal patch using first-generation cell culture technology
- Even though there are great difficulties with validating the superiority of ACI over MF, the potential for a true advantage in terms of function is a real one

- There is observational data to support the hypothesis that ACI is likely to be better than MF if the chondral defect is large, in excess of 4 cm^2
- Patients with these larger lesions may be better served with ACI than with MF

References:

Crawford DC, DeBerardino TM, Williams RJ. NeoCart, an autologous cartilage tissue implant compared with microfracture for treatment of distal femoral cartilage lesions. J Bone Joint Surg Am. 2012;94:979–89

Vanlauwe J, Saris DBF, et al. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee. Am J Sports Med. 2011;39:2566–74.