REGENERATIVE MEDICINE

The clinical benefit of stem cells in cartilage regeneration

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The results of a recent randomized, controlled study suggest than intra-articular injection of autologous stem cells collected from peripheral blood might improve the outcome of surgical approaches to regeneration of articular cartilage after injury. However, questions remain regarding the clinical benefit and feasibility of such an approach.

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In the continued drive for improved methods of articular cartilage regeneration, focus has turned to cell-based therapies, in which the body's own cells are stimulated to contribute to the repair process. Stem cells are seen to have promise in this capacity, owing to their intrinsic ability to proliferate and differentiate into cell types of potential benefit to cartilage formation. A recent study by Saw *et al.*[1] highlights a novel iteration in the development of treatment for cartilage injuries using such an approach. In this randomized, controlled trial (RCT), the culmination of a series of preclinical and proof-of-principle clinical studies, the investigators demonstrate the feasibility of regenerating articular cartilage with a resulting tissue that is similar both grossly and histologically to that of the native human joint.

Currently, arthroscopy is the gold standard method for diagnosis of articular cartilage lesions; however, treatment of these lesions can be varied to include abrasion chondroplasty, subchondral drilling and/or microfracture.[2] Such approaches promote haematoma formation within the chondral defect and migration of mesenchymal stem cells (MSCs) from the bone marrow compartment to the site. MSCs can then undergo metaplasia to form a repair tissue containing a mixture of fibrous and cartilaginous constituents, often referred to as fibrocartilage, which is grossly but not histologically similar to the native hyaline cartilage. The quality of the cartilage repair tissue after microfracture relies on the number and quality of MSCs, which are hampered by the relative paucity of MSCs in the bone marrow compartment.[2–4] Regenerative strategies that involve the use of extended cell culture periods and artificial tissue scaffolds require additional time and cost, as well as more intricate surgery.

Saw *et al.*[1] sought to provide a novel therapeutic intervention that incorporates arthroscopically-assisted subchondral drilling, with the addition of autologous peripheral blood stem cells (PBSC). In theory, the mode of action of PBSCs is based on their migration to the blood-clot scaffold at the site of drilling, followed by differentiation into cartilage components and/or provision of a local stimulatory milieu that promotes other endogenous cells to participate in repair.

In the study by Saw and colleagues,[1] a single surgeon performed arthroscopic subchondral drilling and abrasion chondroplasty in 50 patients with knee joint lesions defined as grade 3 (>50% of cartilage depth, down to calcified layer and/or down to, but not through, the subchondral bone), or grade 4 (lesions with exposed subchondral bone), according to the ICRS grading system.[3] Patients were randomized to either control or intervention groups, each comprising 25 individuals.[1] All patients received intra-articular injections of hyaluronic acid according to a therapeutic protocol often used in osteoarthritis to reduce inflammation and increase viscosity within the joint.[1] Additionally, the intra-articular injections given to individuals in the intervention group contained their own PBSCs, which were harvested, processed, and cryopreserved on the 7th postoperative day (Figure 1).[1] To facilitate PBSC isolation, on the 4th–6th days after surgery, the patients in the intervention group were given injections of filgastrim, a recombinant GM-CSF analogue used to mobilize stem cells into the peripheral blood stream.[1] Thus, the study evaluated

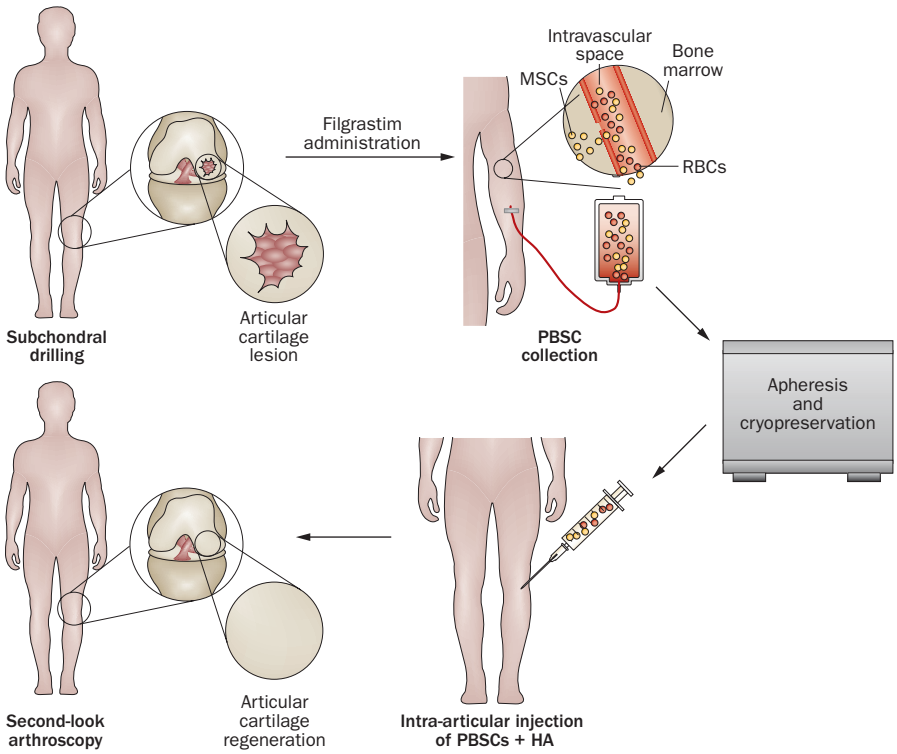

Figure 1 | Schematic diagram illustrating the novel approach to joint-surface regeneration described by Saw *et al.*[1] After subchondral drilling at the site of injury to promote cartilage repair, autologous stem cells are harvested from the patient's peripheral blood and cryopreserved. At various timepoints after surgery, the isolated stem cells are delivered locally in the affected joint by intra-articular injection. This local delivery further promotes articular cartilage regeneration at the site of subchondral drilling. Abbreviations: HA, hyaluronic acid; MSCs, mesenchymal stem cells; PBSC, peripheral blood stem cell; RBCs, red blood cells.

the influence of PBSCs, on a background of hyaluronic acid and subchondral drilling, rather than subchondral drilling alone. Saw *et al.*[5] previously observed that the addition of hyaluronic acid to subchondral drilling improved outcomes in a goat knee injury model; such findings are reflected in the literature, and thus were considered in design of this RCT.

Patients were postoperatively evaluated using patient self-assessment using the IKDC Subjective Knee Evaluation Form,[3] MRI—graded by a musculoskeletal radiologist using a scoring system developed for morphologic MRI evaluation[6]—and second-look arthroscopy, during which chondral biopsies were taken and subsequently graded by two independent, blinded histopathologists.[1]

Saw and colleagues[1] found that IKDC knee scores were not significantly different between the treatment groups ($P = 0.844$). Nevertheless, MRI at 18 months after surgery revealed that knee morphology was significantly better in the interventional group compared with the control cohort ($P = 0.013$).[1] 16 patients from each treatment group consented to second-look arthroscopy and biopsy at 18 months, and histological scores were significantly improved in the intervention group compared with the control group ($P = 0.022$);[1] generally, histological analyses revealed increased numbers of chondrocytes, proteoglycan deposition and collagen type II staining, and reduced collagen type I staining in the intervention group.[1]

Overall, the results of this RCT suggest that PBSCs and hyaluronic acid therapy after arthroscopic subchondral drilling and abrasion chondroplasty markedly improves cartilage regeneration, based on histological findings and MRI scores;[1] however, these improvements did not translate into clinical benefit in regard to pain and mobility,[1] evaluated using a validated instrument. It remains too early to tell whether the long-term benefits of this regenerative strategy justify the additional steps involved, such as mobilization, harvesting and re-introduction of stem cells, and the added patient morbidity associated with these procedures. Nevertheless, that cartilage biopsies seem to show that cartilage tissue quality is improved, in comparison with the fibrocartilage typically observed for other strategies, suggests that long-term benefit is achievable.

The most innovative feature of the study by Saw *et al.*[1] was the local application at the site of injury of autologous PBSCs mobilized from the bone marrow, as opposed to reliance on physiological migration of a limited number of bone marrow MSCs at the site of drilling.[7] Although the exact mode of action of the PBSCs remains unclear, the results of this study are promising. Caplan *et al.*[8] have suggested that MSCs should be renamed 'medicinal signalling cells', given their capacity to perform numerous functions beneficial to cartilage regeneration, including their ability to differentiate into cells associated with cartilage formation and to promote an anti-inflammatory response. Indeed, this theory regarding the expanded role of MSCs might be applicable to the results obtained by Saw and colleagues.[1]

Another interesting feature of the RCT was the use of second-look biopsies.[1] This approach has been explored after autologous chondrocyte implantation,[9] but rarely after intra-articular delivery of stem cells in humans; thus, this RCT provides new insight into the participation of PBSCs in cartilage repair and into the actual morphology of the repair tissue. Nevertheless, the RCT has a number of limitations: the sample size, although sufficiently powered to demonstrate statistical significance, is relatively small when compared with other RCTs. Furthermore, the study was not blinded, as patients in the intervention group were required to provide blood for isolation of PBSCs. The most important critique is that IKDC scores at 2 years follow-up were equivocal between the treatment groups—longer follow-up is, therefore, required. Indeed, the investigators plan to obtain follow-up data at 5 and 10 years,[1] which could provide further information on the efficacy of the approach used.

This study[1] highlights a trend in the application of regenerative medicine for cartilage repair to utilize the body's own restorative capacity. The wide use of platelet-rich plasma (PRP) and conditioned PRP exemplify the new wave of therapies that do not rely on cultivated cells or implanted scaffolds. Whether such therapies alone will accomplish the desired clinical goals remains to be seen.

Evidence-based medicine has become the platform for health-care delivery, on which treatment modalities are created or current protocols are modified. The study by Saw *et al.*[1] provides interesting advances in the regeneration of articular cartilage, from a scientific perspective; however, the approach used could prove difficult to translate into routine clinical practice, given the added cost and patient morbidity, and the demanding amount of work involved. Additional extended RCTs will be required to further assess ultimate clinical applicability of autologous PBMCs in regenerative medicine.

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Competing interests
The authors declare no competing interests.

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