

JOINT RESURFACING: ORTHOBIOLOGICS AND TISSUE ENGINEERING

Mark B. Hurtig, DVM, DACVS

Canadian Arthritis Network Preclinical Laboratory, Guelph, Canada

The term Orthobiologics includes therapeutic proteins, peptides, antibodies, growth factors, receptor blockers or antagonists, viscosupplements, cell-based therapies and devices. In some cases a biologic such as a growth factor is combined with a device such as an implant or suture to hasten osteointegration or drive tissue differentiation.

Orthobiologics has been a controversial topic because it was targeted as a growth sector in the investment industry but yielded poor returns over the last 10 years. In addition, regulation of orthobiologics has been quite different in Europe versus North America, with the former being a more permissive environment for clinical trials and registrations involving biologics. Biologics that we are familiar with such as Adequan™ and Orthokine™ were trialed in human patients before becoming better documented which allowed sales in other countries. In many cases the veterinary market is an afterthought for corporations vying to win regulatory approval.

Cell-based therapies are in a category of their own because of the rapid development of stem cell trials and recently approved therapies using autogenous cells. The seller needs to prove that handling and expansion of these cells before returning them to the patient is safe and efficacious. Unfortunately or fortunately depending on one's point of view, regulation of cell-based therapies in veterinary medicine is cursory so there are many stem cell preparations available to the veterinary community that are poorly characterized. In most cases pivotal efficacy studies have not been done and evidence is at the level of testimonials or uncontrolled trials. Veterinarians who use these products become forceful opinion-makers which helps drive sales but should not become a substitute for independently-conducted controlled randomized trials. Essentially, the application of cell-based therapies in veterinary sports medicine has little evidence-based medicine to support it.

This is very different from the human orthopaedics where cell-based therapies and orthobiologics are approved in many countries. In 1994 Swedish surgeons Lars Pedersen and Mats Brittberg published their report of cell-based cartilage repair in patients after initial studies in rabbits. Genzyme Tissue Repair (now owned by Sanofi) in the U.S.A. commercialized cartilage repair using expanded autogenous chondrocytes cultured in defined media (Carticel™). Cells from a small arthroscopic biopsy were returned to the surgeon who implanted them in a debrided chondral defect under a periosteal or collagen membrane flap that was sutured and fibrin glued to the surrounding cartilage. This second surgery required a full or semi-invasive arthrotomy. Simultaneous second and third generation products were developed in Europe that used press-fit matrices impregnated with autogenous cells (matrix-induced autologous chondrocyte implantation or MACI). Approvals from governments and insurance providers for reimbursement were slow to come but controlled studies using ACI or MACI against the standard of care (arthroscopic microfracture) slowly amassed evidence that long-term outcomes were improved by cell-based therapies. Other commercial entities such as TiGenix™ were quick to create screening algorithms for chondrocyte phenotype and performance (ChondroCelect™) and obtain marketing authorization from the European Medicines Agency and reimbursement from select governments. This was only possible because carefully designed randomized clinical studies showed the superiority of cell-based cartilage repair in large knee cartilage defects greater than 4cm². Pain and function, characterization of the repair volume and tissue quality with MRI, second-look arthroscopy with a biopsy, and quality of life measures with a five year

or more follow up are the accepted outcomes. Another significant factor in the success of these products has been the acknowledgement that ancillary procedures such as unweighting of the one compartment of the knee by osteotomy and staged rehabilitation are equally important to the outcome. A daunting aspect of the validation process has been the cost of maintaining patient registries, clinical trials, and completing long-term assessments. The costs associated with a small clinical trial of this type exceed \$10 million.

Another approach to cartilage repair has been augmentation of arthroscopic microfracture. The advantages of this are a) reduced cost b) only one surgery is needed and c) the limitations of microfracture can be extended. Microfracture is considered the logical choice for symptomatic lesions $<2\text{cm}^2$ and many lesions $2\text{-}4\text{ cm}^2$ in the knee. The liability of microfracture alone is that larger lesions are contraindicated, and the repair tissue is more variable in composition and attachment than cell-based repair. Application of growth factors, chitosan polymers, morselized cartilage, platelet rich plasma or bone marrow aspirate to the surface or within the microfractured bone is aimed at improving recruitment of cells and modulating their behavior to result in better tissue quality. AMIC or autologous matrix induced cartilage repair uses collagen membrane and fibrin glue in a one step arthroscopic procedure that is gaining popularity.

Engineered tissue takes cell-based therapy one step further. Instead of the patient being the bioreactor in which the tissue fully matures, cells are expanded using special media to drive chondrogenesis. Biomechanical or other stimuli are used to partially mature the cartilage to the point where it can be transplanted into the patient. This approach usually involves a bi- or tri-basic construct composed of biodegradable bone substitute on which cartilage is grown. Cell attachment is encouraged with collagen or other coatings. Cell seeding density is a major determinant of the rate of cartilage formation. Mechanical stiffness, rate of degradation and porosity of the substrates influence the cell survival and formation of cartilage which may, under ideal conditions, develop the three dimensional zonal organization of adult cartilage along with the crucial, highly specialized superficial zone. While there are many initiatives in articular cartilage, spinal disc, meniscus and ligament reconstruction, tissue engineering has not achieved clinical success. A notable exception has been the repair of a collapsed trachea in a patient using decellularized antigen-extracted cadaveric trachea repopulated with autogenous stem cells. Since fibrocartilage of the trachea, ear and nose is less specialized than articular cartilage, engineered tissue of that type seems a possibility in the near future.

An example of a successful joint repair initiative in veterinary medicine is subchondral bone cysts of horses, which are by definition an osteochondral defect and probably have a very different biology than chondral defects, though they remain a difficult clinical problem. Combinations of allogeneic juvenile cells, growth factors and bone marrow aspirates have been successful. Taken together this seems to show that renewed endochondral ossification can recapitulate development, so as to produce functional subchondral bone beneath a new layer of cartilage-like repair tissue. Aside from limited use of osteochondral autografts (mosaic arthroplasty) no clearly effective strategies have evolved to address cartilage deficits in the high motion joints of horses or dogs. In many cases subchondral bone quality or deficits create the need for bone and cartilage regeneration in an osteoarthritic environment where a catabolic metabolism has been established. To date there is some evidence that intra-articular administration of growth factors and biologics can reverse these metabolic changes, but intra-articular injection of cells does not effectively repopulate the damaged areas.

In summary, a better understanding orthobiologics therapies is needed before they can be considered validated. Until the quality of clinical trials in human and particularly veterinary medicine is improved the results from our use of this technology will remain unpredictable.

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