Tiered approach to considering orthobiologics for patients with musculoskeletal conditions

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Orthobiologics is a subset of regenerative therapies consisting of biologic substances intended to treat or cure musculoskeletal conditions. They have grown in use and popularity, in part due to a growing evidence-base, but also a result of overexuberance related to a novel field. Numerous devices exist that make the minimal manipulation of autologous concentrated blood, bone marrow and fat derived 'products' accessible for clinical and surgical use in a manner compliant with many national regulatory frameworks. Except for limited surgical cartilage restoration products, however, the absence of formal regulatory 'approved' orthobiologic therapies has led to debate over their utility and subsequent reexamination of the marketing of such products and procedures. The American Medical Society for Sports Medicine has advocated for the responsible translation of orthobiologics into sports medicine practice.[1] Their safe and effective use in clinical practice raises important questions including what level of evidence is needed and under what conditions should orthobiologics be offered to patients for their musculoskeletal maladies.

Evidence-based approaches to patient care frequently use strength of recommendations based on levels of scientific evidence, such as in the Oxford Centre for Evidence-based Medicine. Level 1 evidence suggests high scientific rigour, whereas levels 2–5 are less certain. Many procedures in orthopaedics and sports medicine fall within level 3 due to the invasive nature of such interventions, which can make randomised controlled trials unethical or impractical.[2] As a result, recommending novel orthobiologic therapies to patients as part of clinical and surgical practice requires both an assessment of the level of clinical evidence and an assessment of patient-level considerations. Based on the clinical evidence to date, current orthobiologics can be categorised into three tiers of recommendations (figure 1).

TIER 1: PROVEN SAFETY WITH ROBUST EVIDENCE

With respect to currently utilised orthobiologics, trials of platelet rich plasma (PRP) to treat knee pain from osteoarthritis as well as certain tendinopathies (eg, rotator cuff and lateral epicondyle) demonstrate strong safety and reasonable efficacy.[3 4] Well-executed systematic reviews confirm these findings with other conditions such as gluteal tendinopathy not far behind.[4] Therefore, it is reasonable to consider PRP treatment for these indications alongside other standard of care treatments. However, PRP has not been validated for many musculoskeletal conditions such as Achilles tendinopathy, ankle osteoarthritis and may be less effective in severe knee osteoarthritis. Therefore, clinicians should be familiar with the evidence for and limits of PRP before generalising indications for its use to other maladies that might be better considered as a tier 2 alternative.

TIER 2: PROVEN SAFETY WITH GROWING EVIDENCE

The more pressing challenge is for orthobiologics where safety has been demonstrated and evidence for efficacy is growing but remains insufficiently robust (level 2 and level 3 evidence base). It may be suitable to try tier 2 alternative therapies when other options have failed, or when the alternative treatment such as surgery is higher risk, uncertain or undesired by the patient.[5] Bone marrow aspirate concentrate (BMAC) to treat knee osteoarthritis and osteonecrosis of the femoral head are examples.[6 7] Early clinical trial results support BMAC as an effective biologic to reduce pain

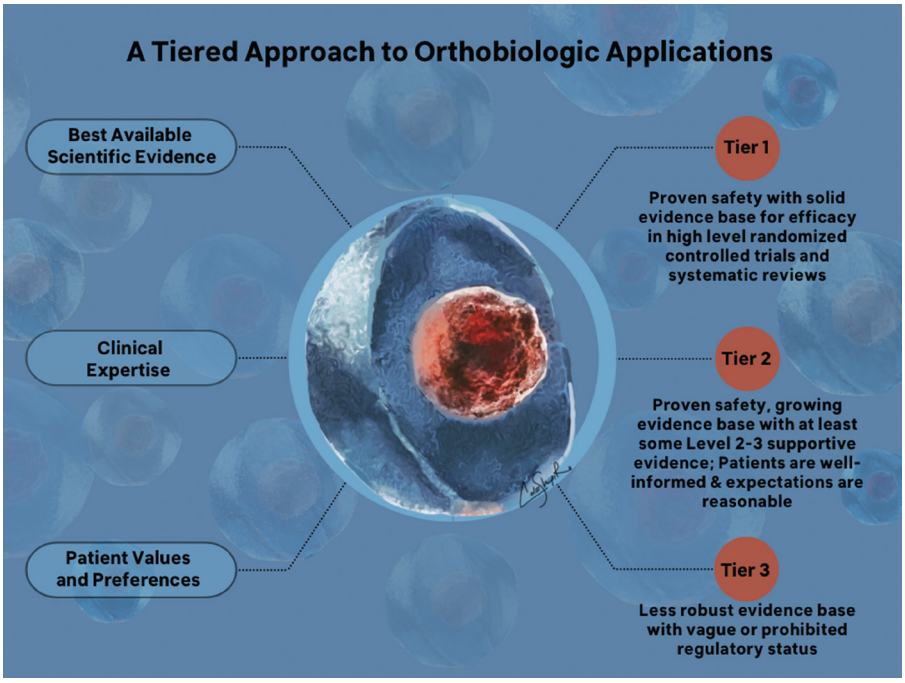

Figure 1 A tiered approach to orthobiologic applications. The ultimate goal of evidence based medicine is to use the best evidence to improve the care of individual patients. However, applying best evidence to clinical practice is not always straightforward. As a result, the best available scientific evidence is often combined with other valuable factors including the clinician's expertise and patient values and perspectives.

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and improve quality of life though not necessarily superior to other standard of care treatments.[7] Additional obligations for such tier 2 recommendations require that patients are well-informed while expectations and costs are not unrealistic.[8] Although patient preferences are a central feature in shared decision-making in healthcare and regulatory decision-making, patient preferences and professional judgement are not meant to substitute clinical safety and efficacy data during clinical decision-making.

TIER 3: LESS EVIDENCE AND REGULATORY APPROVAL STILL REQUIRED

It is easier to discourage use of novel therapies with limited evidence (levels 4 and 5 evidence base). Tier 3 orthobiologics with insufficient study subject numbers, non-randomisation or inadequate controls suggest the scientific support is incomplete for such treatments. Examples include wide-ranging perinatal injectables harvested and/or manufactured from heterogeneous sources such as umbilical cord blood, Wharton's jelly and amniotic tissues.[9] Consequentially, less validated orthobiologics should only be offered within an investigational capacity and reviewed by an institutional review board (IRB) with appropriate regulatory oversight.

SHARED DECISION-MAKING AND NEXT STEPS

In settings where orthobiologics with levels 2 and 3 evidence are recommended, there is an ethical imperative to conduct stronger research to clarify their use and efficacy. More robust level 1 studies and data from biologic outcome registries are needed.[10] Sports physicians should balance the existing evidence with the clinical situation and patient preferences when considering orthobiologics with mid-level clinical evidence (figure 1). As more clinical trials are performed and more robust evidence emerges, scenarios by which providers may recommend novel procedures to their patients will become more clear. Until then, clinicians should continue to offer honest and thoughtful approaches to patients with chronic orthopaedic conditions, especially when considering less well-studied orthobiologics.

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