Orthobiologics: Osteoarthritis

Iain R Murray, Martyn Snow, Cosimo De Bari and Andrew W McCaskie

Iain Murray is a Consultant Orthopaedic Surgeon at Edinburgh Orthopaedics and Honorary Senior Lecturer at The University of Edinburgh. He is a member of the Orthopaedics and Musculoskeletal Therapies Committee for the International Society for Cell and Gene Therapy (ISCT) and the Biologics Association. He is an Associate Editor of the Bone and Joint Journal (BJJ).

Martyn Snow is Professor of Regenerative Medicine at Keele University and Honorary Professor of Chemical engineering at the University of Birmingham. He is a Consultant Knee and Shoulder Surgeon at The Royal Orthopaedic Hospital in Birmingham and The Robert Jones and Agnus Hunt Hospital in Oswestry. His clinical and research interests include cartilage repair and joint preservation.

Cosimo De Bari holds a Clinical Chair in Experimental Medicine and Rheumatology at the University of Aberdeen. He is Director of the Aberdeen Centre for Arthritis and Musculoskeletal Health (a EULAR Centre of Excellence in Rheumatology) and Deputy Director of the Versus Arthritis Tissue Engineering & Regenerative Therapies Centre.

Osteoarthritis (OA) affects around 8.5 million people in the UK alone[1] and the success of treating end-stage disease with joint replacement is well known. The treatment of osteoarthritis at earlier stages is less clear and represents an important area of global unmet clinical need. Around half of the 8.5 million people with OA in the UK are between 45-65 years of age, in whom knee replacement is known to have a higher risk of failure, with around 33% of primaries performed between the ages of 50 and 55 requiring revision[2].

The unmet need coupled with the limitations of conventional arthroplasty have led to great interest in the development of new treatments for early stage OA, in order to modify symptoms and/or modify the natural history, with the aim to delay replacement.

It is important to appreciate that OA at early stages is heterogenous, both in terms of disease progression and pathogenesis, with distinct clinical phenotypes[3]. Stratification of patients in early-stage OA therefore offers a 'window of opportunity' for intervention[4] and this can increasingly be characterised by biomarkers and imaging e.g. MRI. We will review the therapies generally considered orthobiologics, which will exclude some types of regenerative therapies, for example those aimed at treating defined cartilage lesions before OA, such as autologous chondrocyte implantation, which has NICE approval[5].

Orthobiologic therapies

In recent years, novel intra-articular injectable therapies have gained increasing attention with both the biomedical community and the public[6]. The most widely available Orthobiologic therapies are autologous blood products, and cell therapies prepared from bone marrow and adipose tissue. Autologous blood products include platelet-rich plasma (PRP) preparations and autologous anti-inflammatory (AAI) preparations. Cell therapies can broadly be divided into those harvested and delivered at the point of care (including concentrate of bone marrow aspirate, commonly abbreviated to BMAC, stromal vascular fraction, (SVF) and microfragmented adipose tissue (MFAT)) and those requiring a degree of processing considered 'more than minimal manipulation' or a period of cell culture in a laboratory (Figure 1).

Autologous blood products

Platelet-Rich Plasma (PRP): Growth factors contained in PRP act on pathways that can dampen the inflammatory response. In addition, growth factors present in PRP have been shown to stimulate collagen synthesis, extracellular matrix production, and promote cell proliferation in laboratory conditions[7]. The use of PRP in OA has been studied in more than 30 prospective RCTs, with most involving the knee. The data has been reported in multiple meta-analyses[8-12] demonstrating improved symptom control, favoring PRP preparations over controls (including hyaluronic acid, saline and corticosteroid), when only prospective randomised studies were included[8-12]. There are no safety concerns but as yet there is no evidence demonstrating restoration or regeneration of articular cartilage[8-16]. Recent professional guidelines including the AAOS[17],

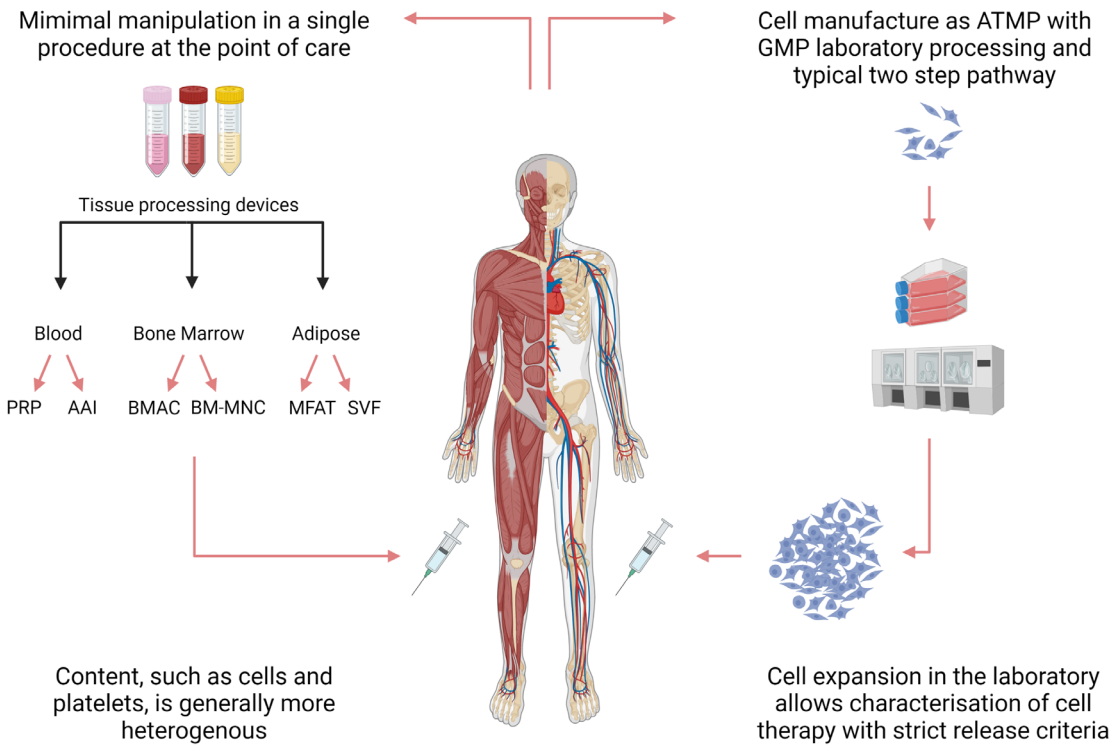

Figure 1: Cell therapies can broadly be divided into those harvested and delivered at the point of care, and those undergoing laboratory processing including cell culture and expansion. *(ATMP, Advanced Therapy Medicinal Product; GMP, Good Manufacturing Practice). Created with BioRender.com.*

Andrew McCaskie is Professor of Orthopaedic Surgery and Head of the Department of Surgery, University of Cambridge, with a clinical interest in lower limb. He is Director of the Versus Arthritis Tissue Engineering & Regenerative Therapies Centre and an Editor of Bailey and Love's Short Practice of Surgery.

American College of Rheumatology (ACR)[18], OA Research Society International (OARSI)[19] and NICE[20] have reported "inconsistent evidence" and limited reporting of variables critical to outcome e.g. the platelet count of PRP administered. As such, AAOS downgraded their support of PRP to 'limited' and NICE recommended the procedure only be used with special arrangements for clinical governance, consent and audit or research. ACR and OARSI "strongly recommend against" the use of PRP for OA[18,19].

Autologous anti-inflammatories (AAI): AAIs focus on concentrating white blood cells, or the anti-inflammatory factors they release, rather than on concentrating platelets. Autologous conditioned serum is a cell free serum collected from incubated WCCs with high concentrations of anti-inflammatory cytokines. Two RCTs have reported improvements in PROMs and pain scores in patients receiving autologous conditioned serum for knee osteoarthritis over placebo[21,22]. Autologous Protein Solution (APS) is generated from leukocyte rich PRP that is mixed with polyacrylamide beads and centrifuged to release inflammatory cytokine antagonists from WCCs. A recent RCT has reported improvements in functional and pain scores over placebo[23]. AAIs were not specifically evaluated in the most recent AAOS, ACR or OARSI guidelines.

Cell based therapies

1. Point of care cell-based therapies

BMAC and bone marrow mononuclear cell (BM-MNC) preparations: BMAC contains bone marrow cells, small tissue fragments, and blood from venous sinuses[24]. The MSC concentration is low, comprising 0.001% -0.01% of all mononuclear cells[25]. Related preparations include BM-MNCs which are isolated and enriched from bone marrow aspirate by chemical density gradients[26]. The nucleated cells in BMAC may deliver cytokines and growth factors at the delivery site[27]. There is little support for restoration of degenerate cartilage and no reports of long-term survival or meaningful engraftment of delivered cells. A small number of prospective randomised studies have evaluated the use of BMAC or BM-MNCs in the setting of OA, with conflicting results[26,28-30].

Microfragmented adipose tissue (MFAT): Microfragmented fat products are prepared via non-enzymatic mechanical disruption of lipoaspirate into small particles partially releasing cells from the extracellular matrix. The proposed mechanism relates to a role for cushioning and support, as well as the capacity for the cells present to release a range of immunomodulatory and trophic factors. >>

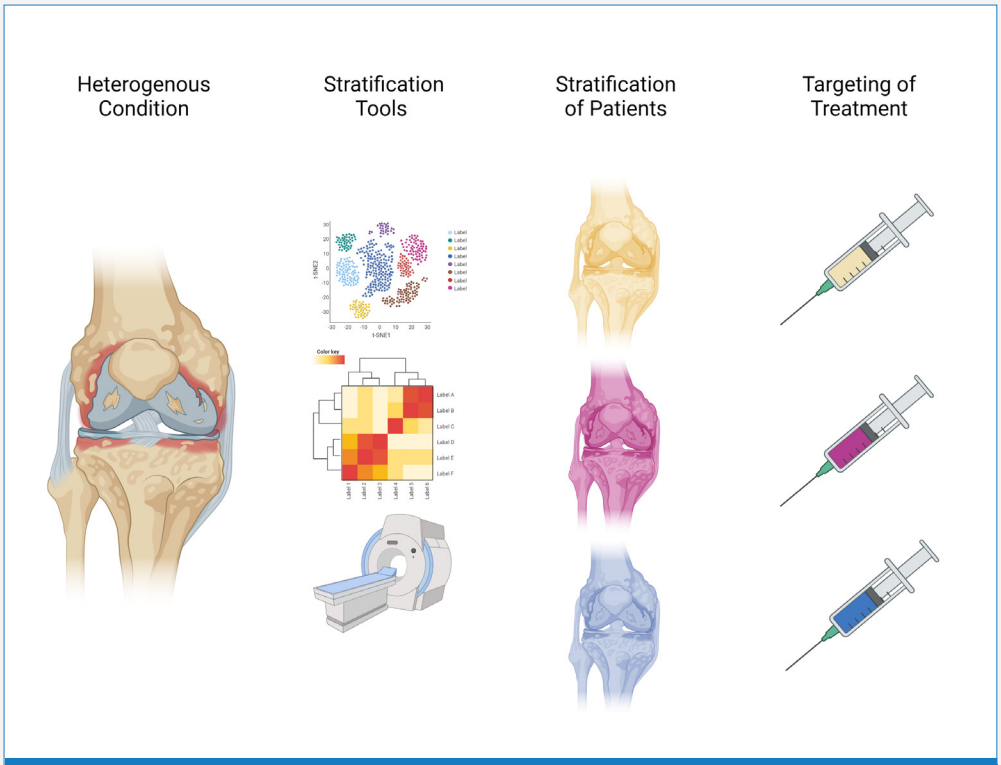

Figure 2: Schematic showing the heterogeneous nature of osteoarthritis and how stratification tools can help stratify patients to targeted treatments. *Created with BioRender.com.*

There are a large number of non-randomised studies reporting promising results[31-36], but no completed RCT of injection alone for large joint OA has been published.

Stromal vascular fraction (SVF): SVF is prepared from adipose tissue, typically by enzymatic digestion, and aims to harness the potential of the MSCs and other cell types. Two RCTs have reported improvements in PROMs with SVF over controls, with one study reporting improvement in MRI cartilage parameters[37,38].

Point of care manufacture

The Medicines and Healthcare products Regulatory Agency (MHRA) is currently considering a new framework to enable the safe development of point of care (POC) products. This will include the use of device technologies for isolating tissues and cells or blood components, and may have a significant impact on their future use in the UK[39].

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2. Cultured Cells

Cultured 'mesenchymal stromal cells' (MSCs): In contrast to POC manufacture, laboratory culture allows for the administration of millions of MSCs. They are classified as an Advanced Therapy Medicinal Product (ATMP) and are highly regulated (MHRA) and generally more expensive to produce than POC products. Overall, published prospective RCTs evaluating culture expanded MSCs for knee osteoarthritis reported a positive effect on patients' symptoms with some advanced imaging parameters indicating improvements in cartilage quality. The vast majority of studies only report outcomes to one year and larger and longer randomised controlled studies are required[40-47].

Patient stratification and the challenges of orthobiologics

The heterogeneity in both patients with the early stages of OA (progression and pathogenesis) and in orthobiologic preparations makes the interpretation of findings from clinical studies challenging. Moving forward, sound clinical evidence will benefit from reduced heterogeneity in relation to manufacture, potency and delivery. As always in medicine one solution does not fit all and the stratification of patients with OA will contribute to our ability to develop more targeted interventions (Figure 2). To achieve widespread adoption, in addition to effectiveness, cost-effectiveness is important, particularly in therapies looking to alter the natural history of OA, over and above symptom relief. In conclusion, we are at the start of an era of unprecedented opportunity for orthopaedic and musculoskeletal therapy development, not least for patients suffering from OA. ■

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