



ELSEVIER

Biologics in shoulder and elbow surgery

With the proliferation of biologic treatments to treat soft-tissue disorders, often about the shoulder and elbow, and the concomitant proliferation of clinics specifically devoted to providing these biologic treatments, we are honored this month to have 2 review articles on the state of the art written by 2 of the absolute experts in the field, Jason L. Dragoo and Scott A. Rodeo. Below, Drs. Dragoo and Rodeo introduce the topic, and hopefully, their review articles will contribute to our current knowledge and understanding of this important topic.

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COMMENTARY

The New York Times, May 13, 2019: “Stem Cell Treatments Flourish With Little Evidence That They Work”



It is not uncommon to see billboards in almost every community advertising “stem cell therapy.” Biologic therapy is also discussed frequently in the press, including this recent piece in *The New York Times* describing the continued proliferation of “regenerative medicine clinics” around the United States. There appears to be an obvious disconnect between this growing number of stories, often describing the indiscriminate and inappropriate use of unproven “biologic treatments,” and the increasing utilization of these biologics by our patients and colleagues.

An all-too-common scenario is a patient who brings in stacks of printouts from the Internet with often confusing and contradictory information about cell therapy to treat his or her painful orthopedic condition. What should we do as clinicians? Should we recommend one of these “biologic” treatments for the patient, and if so, which one? To be honest, many of our current treatments for tendinopathy, early osteoarthritis, and muscle injury are often inadequate, and autologous therapies such as platelet-rich plasma (PRP) are generally safe.

However, if one wants to use biologic augmentation, we are then faced with a dizzying array of questions and considerations:

1. What type of PRP do we use?
2. Would cell therapy be better?
3. If cell therapy is used, what cell source do we use? Bone marrow? Adipose tissue? Amnion? Placenta?
4. Do we use a single injection or serial injections?
5. What is the optimal post-treatment regimen? Do we recommend activity modification? Do we limit the use of nonsteroidal anti-inflammatory drugs?

Given all of these important questions related to biologic therapies, in this issue of the *Journal of Shoulder and Elbow Surgery*, we have summarized the current status of biologic approaches for common shoulder and elbow problems in 2 review articles. Perhaps most important, we have discussed areas where the current evidence base is weak and controversial, and we have pointed out areas where further studies are required.

There is no doubt that biologics have great potential for improving tissue healing and repair. However, many limitations currently exist, including the significant variability between product formulations. In addition, a large number of patient-specific factors affect the composition and biologic activity of products, including age, sex, medical comorbidities, concomitant medications, and genetic and

epigenetic factors. This variability as well as unpredictability of the “biologic product” is then added to the variability of the underlying pathology being treated.

Consideration of these factors makes it clear that “one biologic product does not fit all.” In other words, the same biologic formulation would not be expected to have the same positive effect on diverse tissue types or pathologic conditions. Lastly, biologic treatment, for any condition, can only be successful once we understand the underlying biology of the condition. We need to identify what the goal of our treatment is. Is it to stimulate cell proliferation, increase matrix synthesis, promote angiogenesis, decrease inflammation, stimulate matrix remodeling, or simply to inhibit nociceptive mediators and thus pain? Only once we answer these fundamental questions can we begin to match the optimal biologic formulation with the specific tissue and pathology being treated.

A very important factor affecting our ability to use biologic treatments is the regulatory status. Whereas PRP is not regulated by the US Food and Drug Administration, the use of cell therapy approaches in the United States and some other countries is subject to such US Food and Drug Administration regulation. Most cell therapy products are regulated under Title 21 of the *Code of Federal Regulations*, part 1271, section 361. Certain autologous cell formulations may be exempt from regulation as a biologic drug (section 351) as long as they meet all of the following criteria:

1. Minimally manipulated
2. Intended only for homologous use
3. Not combined with another article
4. Either have no systemic or metabolic effect or be for autologous use or allogeneic use in first- or second-degree blood relative

The critically important point is “minimal manipulation,” which is defined as processing that does not alter the

relevant biological characteristics of cells or tissues. This mandate limits the processing of tissue to the “point of care” (the operating room or clinic where the tissue was harvested). This means that we cannot take the material to the laboratory for culture expansion, in contrast to some countries such as the Republic of Korea and Japan, as well as some European countries, where cells can be cultured to isolate and then increase the population of “desired” cells. This has led many patients to pursue “medical tourism” where they travel overseas seeking “stem cell treatment.” There is always a risk of infection or complications when patients receive treatments in less regulated environments, and it is often unclear what is actually being injected.

Our summaries will provide the reader with up-to-date clinical data, and we hope these will also stimulate further research in this important and growing area of musculoskeletal medicine.

Disclaimer

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