Preliminary Retrospective Analysis of Case Reports of AmnioFix® Injectable Human Amniotic Membrane Allograft in Soft Tissue Injuries and Inflammatory Conditions

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Abstract

A brief review of the AmnioFix Injectable was conducted by interviewing early clinical users of the material. This developed an initial set of impressions that will guide further development and use of the material. These impressions include:

- The patient's underlying complaints of chronic pain from soft tissue injuries resolved completely 42% of the time; with partial and complete resolution occurring some 62% of the time. The remaining 38% of patients saw no improvement in underlying soft tissue injuries or inflammation.
- The AmnioFix Injectable injection is relatively well tolerated without apparent significant or major safety issues.
- The material appears to work better in patients with recent (i.e. less than one year old) inflammatory conditions than in patients who have prolonged underlying problems in excess of one year.
- Pain from inflammation as a side effect has been associated with the injection approximately 60-65% of the time. Pain from inflammation appears to be worse within the first 24-36 hours and then gradually and subsequently resolves to baseline levels of pain or below.
- Occasionally, soft tissue swelling has been associated with injection of the material regardless of the amount of material or technique used. The etiology of this swelling remains to be elucidated but is currently under study. Swelling in all cases resolved over one to three weeks as the material was absorbed. Swelling, as identified by physicians, is associated with a fluctuant fluid-like area of inclusion which may be related to simply the injected material itself.
- Resolution of underlying patient pain from inflammation and symptoms can occur within one to two weeks, but typically the underlying pain and inflammation associated with the condition gradually decreases over the first four weeks.
- Efforts to prophylactically address the pain from inflammation and/or swelling may help and could be studied further.

Introduction

Human amniotic membrane has been used clinically in a variety of applications for over 100 years.[1] Applications have included use in a number of specialty areas, including ophthalmology, wound covering / healing, dermatology, general and orthopedic surgery, and others. In this decade, research by Surgical Biologics, LLC. has produced several configurations of dehydrated, non-decellularized human amniotic membrane for clinical use, with widespread acceptance of the material in a number of applications. These include anterior eye (conjunctival) repair, wound covering / healing, dura covering / healing, periodontal surgery and other applications.

Recently, further processing of human amniotic membrane with a micronization process to produce a powder has been completed. Dispersion of the powder into suspension with saline solution at the point of care has created both new means of delivery and new markets. In vivo and in vitro studies have shown that the biochemical properties of amniotic membrane help to reduce inflammation and enhance soft tissue healing.[1] Injecting areas of soft tissue injury is now possible.

AmnioFix Injectable is composed of micronized amniotic tissue packaged to optimize clinical ease of use. The proprietary PURION® Process used by MiMedx Group to prepare the dehydrated non-decellularized amniotic membrane has been documented to retain the amniotic growth factors and cytokines inherent in this tissue.[2] The result is an injectable product that potentially offers a variety of properties including:

- a combination of growth factors unique to amniotic tissue
- the ability to reduce inflammation in tissues near the injection site
- an enhancement of the normal wound-healing process

Beginning in the fall of 2011, MiMedx Group embarked on a limited commercial launch of AmnioFix Injectable. This included both commercial release of the material and the provision of evaluation product to clinicians. Materials shipped to these physicians included:

- Product package with sample vial for each sample.
- Patient authorization to release information on the patients who will receive the material.
- Directions for use within the package for the doctors.
- Product information for the patients within each box.

Sample sizes distributed included 0.5 cc, 1.25 cc, and 2.0 cc vials.

Clinicians were identified from sales and tissue utilization records and were contacted to retrospectively review the clinical results of using the material. MiMedx conducted this outreach to interview physicians regarding their clinical use and experience with the material when administered as an injection for the recommended use of soft tissue injuries and inflammatory conditions.

Materials and Methods

As of the date of this document, a limited number of clinicians located at different locations were identified who have multi-patient experience and use of the injectable and who were willing to conduct a detailed post-market interview. Clinicians were called and scheduled to be interviewed. They were asked to have available, during the interview, immediate access to the patient medical records of those who had been administered the material.

A total of 26 patient treatments from 5 different physicians were eventually accumulated, representing a number of different conditions. All patients received only a single injection of the micronized amniotic membrane allograft. The data collected represents an informal discussion performed with the implanting physician who has used the injectable product.

The purpose of the interviews was to specifically do the following:

- Collect general information regarding handling properties, ease of use, and practical operational issues in using the AmnioFix Injectable product.
- Identify safety issues and parameters to be used ultimately in patient informed consent and IRB review documents.
- Evaluate the side effects and possible complications that might be initially identified with the material.
- Establish estimates of effectiveness in using the material compared with usual care in order to gage overall effectiveness.
- Establish preliminary sample size estimates for anticipated clinical trials.
- Assess the duration and time course of effect to estimate the total time to healing when using the material and to estimate the duration of any future proposed formal research studies.

Discussion with the physicians focused on the following key pieces of information:

- Injuries or conditions treated
- Patient selection and demographic information
- Vial size/dose used
- Preparation techniques
- Administration techniques
- Relative efficacy/effectiveness perceived by the physicians
- Time to healing
- Safety/side effect information

Findings

The population selected by the clinicians for use of the material ranged in age from 35-70 years old with a mixed male-female demographic. Physician interviews were limited to physicians who used the material for musculoskeletal, soft tissue and tendon injuries and inflammatory conditions as suggested by the accompanying marketing material.

Injuries or conditions identified by the physicians using the material include (number of cases):

- Plantar fasciitis (12)
- Epicondylitis (medial and lateral) (8)
- Toe joint related issues such as hallux limitus (2)
- Achilles tendonitis
- Biceps tendonitis
- Triceps tendonitis
- Acromioclavicular joint area inflammation

The level of inflammation encountered in these patients was predominantly chronic, poorly or non-healing inflammatory conditions of the soft tissues that had not previously responded to standard-of-care measures. These typically included reduced range of motion, physical therapy, nonsteroidal anti-inflammatory drugs, and steroid injections. *This represents a significant bias in the selection of these patients, since selected patients were by definition relatively refractory to standard of care treatment attempts for a variety of reasons*.

The etiology of the injuries was for the most part related to repetitive injury in patients with non-podiatric conditions. For podiatric conditions, plantar fasciitis predominated, and etiologies common in patients presenting with plantar fasciitis such as prolonged standing, obesity, recurrent trauma (running) in patients were noted.

The amount of material typically used for all indications was in the range of 0.5-2.0 cc. For foot/podiatric conditions 0.5 cc were typically used.

Side Effects

Side effects appeared to be limited to only pain from the injection at the injection site and/or moderate swelling without direct correlation.

Pain

Pain from the injection was noted to occur in approximately 57% of patients, with symptoms being significant enough to require treatment or pain medicine in only 19% of cases. The remainder of cases had either no pain or no report of pain in the medical record.

The response was noted to be variable with respect to both time and duration of pain resolution. Physicians interviewed noted that there was a fairly wide response regarding an

individual's pain in the same types of injections. Several physicians also noted that similar pain can be seen in giving patients any injection of a substantial amount of material

Swelling

Swelling was noted at the injection site in approximately 23% of patients. The exact etiology of this swelling is not clearly known, but suspected reasons include slow resorption of the liquid and possible influx of either fluid and/or cells as part of the healing process.

Frank evidence of inflammation, with redness, heat, tenderness, etc. was only rarely noted in our case reports.

Overall Effectiveness

Symptom Resolution

With respect to overall effectiveness, i.e. degree of symptom resolution, the material was noted to produce complete resolution of the underlying symptoms in 42% of cases, and complete or partial resolution of symptoms in 62% of cases. The remaining 38% of patients saw no improvement in underlying soft tissue inflammation.

All of the assessments of success were measured by pain measurement outcomes and not by functional measurement outcomes. Patients that were in the acute phases of injury seemed to respond to the AmnioFix Injectable treatments more often than those in more chronic phases of injury.

Healing Time Course

With respect to ultimate duration of symptoms until no further change occurred, patients who did show improvement generally improved over a period of from one to four weeks, but some patients demonstrated improvement and/or resolution in as long as six or more weeks.

For the most part, when patients did show improvement, physicians noted that healing or a plateau in response occurred within 4 weeks. A minority of cases continued to resolve at longer intervals between 4 weeks and 3 months.

Anecdotal Comments

Clinicians working with the material have suggested that efforts to reduce both swelling and movement might reduce the side effects.

Some physicians reported the use of standard of care methodologies post-injection including the application of ice to the injection site, and the use of nonsteroidal anti-inflammatory drugs prophylactically. Similarly, clinicians commented that weight reduction and/or immobilization

of the injected area seemed beneficial also. For example, one might use a CAM walker for plantar fasciitis or an ace wrap in an epicondylitis patient may be helpful.

Other comments made included the recommendation that dosage might need to be larger in some cases, with a starting dose of 0.75 cc rather than 0.5 cc initially. Most clinicians felt that the 2.0 cc size was too large from a volume perspective.

Discussion

Detailed interviews of the clinicians involved who used the material, as well as other external reports from physicians not interviewed in this retrospective clinical record review, have resulted in several conclusions regarding the use and effectiveness of the AmnioFix Injectable human amniotic membrane allograft material. These include:

- The patient's underlying complaints of soft tissue injury and inflammation resolve completely, even in these chronic cases, 42% of the time and with partial and complete resolution occurring some 62% of the time. The remaining 38% of patients saw no improvement in underlying soft tissue injury and inflammation.
- The injection is relatively well tolerated without apparent significant or major safety issues.
- The material appears to work better in patients with recent (i.e. less than one year old) soft tissue injuries and inflammatory conditions than in patients who have prolonged underlying problems in excess of one year.
- Pain from the injection as a side effect has been associated with the injection approximately 60-65% of the time.
- Soft tissue swelling has been associated with injection of the material, which again seems to occur inconsistently, regardless of the amount of material or technique used.
- Resolution of underlying patient pain from inflammation and symptoms can occur within one to two weeks, but typically the underlying pain and inflammation associated with the condition gradually occurs over the first four weeks with some patients requiring four to greater than six weeks for resolution.
- Efforts to prophylactically address the pain from the injection and/or swelling may help, and could be studied further, such as using non-weight bearing strategies, reducing range of motion of the affected tendons, using ice on the injection site, or using an ace wrap or related dressing.

Conclusion

Overall, the AmnioFix Injectable material appears to be a moderately effective treatment for chronic and acute soft tissue injuries and inflammatory conditions. The material is well tolerated, though occasionally painful, and so far has had no significant reported side effects other than those mentioned above in usage reported to the company to date.

A randomized control trial with usual standard of care would better evaluate and define the effectiveness of this material in selected types of pathology and should next be undertaken. MiMedx is actively pursuing formal, IRB approved studies using the material for plantar fasciitis and epicondylitis, and hopes to complete these studies within the next 6 months.

References

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