A New Approach in OA: Dietary Management

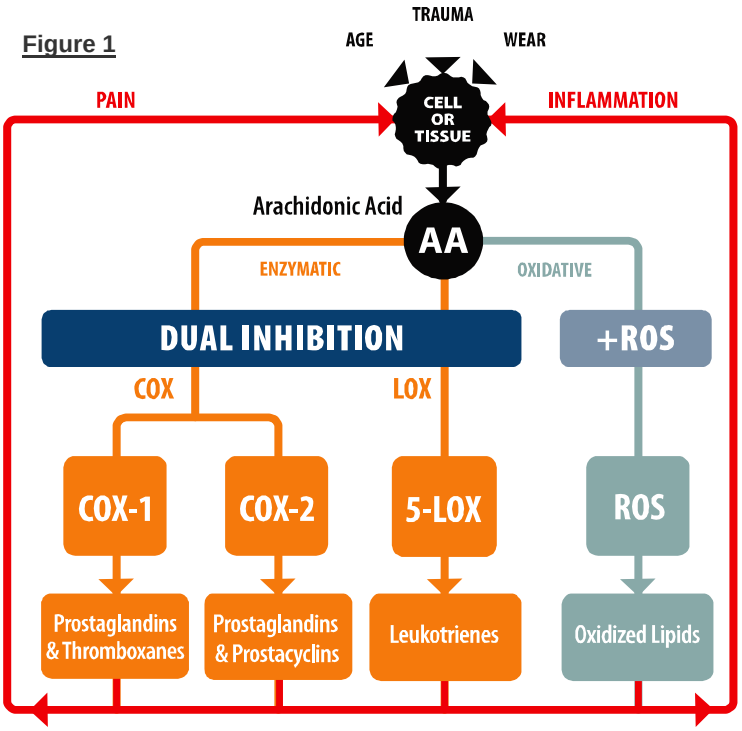
Recent News and Trends

With the recalls of selective COX-2 inhibitors and FDA's recommendation to place a "black box" warning on the labels of most Rx and OTC anti-inflammatory drugs, physicians are changing their prescribing habits due to heightened safety risks. [1] Many physicians have returned to prescribing older NSAIDs, including OTC products, even with their gastrointestinal side effects. Some physicians have even stopped prescribing drugs for OA altogether. Patients are finding more information on osteoarthritis (OA) from the media, often unbalanced or sometimes untrue, and many have chosen self-management without much regard for potential side effects. Originally, OA was thought of as a degenerative disease associated with joint injury and aging. However, recent insights have shown that after initial damage, OA progresses due to an excess of arachidonic acid (AA) metabolism that increases inflammatory responses. Thus, OA is a metabolic deficiency disease which responds to dietary management.

The Problem: Balancing Fatty Acid Metabolism to Manage Disease

While drugs focus on treating or masking symptoms, OA patients need help to manage the metabolic processes of OA, thereby normalizing the levels of key metabolites. The initial event in the development of OA is damage to joints through traumatic injury or overuse and release of phospholipids from damaged cell membranes which are converted to arachidonic acid (AA) by phospholipase A_2, a necessary fatty acid building block for membranes in the body. Metabolism of AA also generates necessary fatty acid molecules for platelet aggregation, maintenance of stomach mucosa, organ function, proper blood flow, urine production, blood pressure, tissue repair, and viral immunity.[2-3] AA is metabolized via the COX [cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)] and LOX [5-lipoxygenase (5-LOX)] pathways into thromboxanes, prostaglandins, prostacyclins, and leukotrienes (Figure 1)[4]. In addition, AA is converted via an oxidative mechanism into F2-isoprostane, malondialdehyde, and 4-hydroxynonenal molecules, which directly degrade cartilage and induce other inflammatory proteins.[5] As aging occurs, however, AA both from the diet and the conversion of phospholipids accumulates in excess in the body. The metabolism of excess AA to the above metabolites and its associated cyclical inflammation is what propagates the disease and leads to cartilage degradation over time.[6] In this metabolic sense, inflammation is not merely a symptom of OA, rather this inflammation cascade is the essence of the disease itself. Managing the AA metabolic processes can ultimately ease functional stiffness and inflammation, and restore functional mobility.

Figure 1



The balance of AA metabolites is very important to avoid deleterious effects on normal functions in the body. As an example, two of the most important AA metabolites for maintenance of normal kidney and cardiovascular function are thromboxanes and prostacyclins.[7] Thromboxanes, produced by platelets via the COX-1 enzyme, are involved in proper platelet aggregation and also cause vasoconstriction in the vasculature. Prostacyclins, generated from AA via COX-2, are required for vasodilation of vessels and are antagonistic to thromboxanes.[8] If the production of prostacyclins is selectively inhibited to a high level, then thromboxanes dominate by constricting arteries and arterioles causing decreases in urine perfusion in the kidney and blood flow in the microvasculature around the heart. Decrease in urine perfusion leads to increased systolic blood pressure and peripheral edema, while decreased blood flow to the heart can starve the tissue of oxygen and nutrients, especially if a person has plaque accumulation. Both of these events lead to stress on the cardiovascular system, which contribute to increased incidence of heart attack and stroke. These products of enzymatic AA conversion must remain balanced to allow the body to function properly.[9]

A New Approach: Dual COX/LOX Mechanism of Action

A new approach on the market for OA is through dual COX/LOX mechanism of action (a.k.a. dual inhibition).[10] This approach helps to restore the balance of fatty acids, by damping AA metabolism non-selectively across the COX and LOX

pathways, thereby minimizing common side effects. This balanced down-regulation, though weaker than traditional NSAIDs and selective COX-2 inhibitor drugs, allows the body to produce AA metabolites at relatively equal levels to maintain function within the body. Dual inhibitors may provide an answer for the imbalances that traditional NSAIDs (COX-1 imbalance) and selective COX-2 inhibitors (COX-2 imbalance) cause in AA metabolism. A prescription product utilizing this new approach is a medical food product called Limbrel™. Medical foods are an FDA regulated class of foods meant to provide distinctive nutrition requirements or to restore metabolic balances, and in this case, the balance between COX-1 and COX-2 activity. Limbrel has been gaining wide acceptance based on its safety and ability to manage the metabolic processes of OA using food-based ingredients. It contains concentrated levels of food-based ingredients called flavonoids which also act as a potent antioxidant to limit oxidative conversion of AA to other damaging fatty acid products affecting cartilage degradation. Licofelone from Merkle of Germany is currently the only prescription drug dual inhibitor in phase III trials, and is not expected to be approved and marketed for a number of years. Its safety profile per published studies shows fewer gastrointestinal events than NSAIDs and selective COX-2 inhibitors.[10] Judging from the current spate of patents by major pharmaceutical companies, we can expect to see more dual inhibitors as either drugs or medical foods in the future for the treatment or dietary management of OA.

Medical Foods

FDA regulates "Medical Foods" as a discrete class of medical products for the dietary management of diseases or medical conditions, when a nutritional or metabolic imbalance characterizing the disease or condition can be restored with nutrients, specially formulated in an oral administration taken under a physician's supervision. Therefore, medical foods are different from drugs, because they work on the underling metabolic process of a disease or condition, instead of merely masking or modifying its symptoms. The governing definition of medical foods is listed in Section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)) which states that a medical food is *"a food which is formulated to be consumed or administered enterally [or orally] under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."* Medical foods are safe because one of their other statutory requirements is that their ingredients have GRAS (Generally Recognized As Safe) status (see below). Medical foods have been distributed in hospitals as special nutritional formulations containing vitamins, trace elements, minerals, fatty acids, flavonoids and amino acids for diabetes mellitus, renal disease, pernicious anemia, gastrointestinal disorders, cachexia, chronic pancreatitis, elevated homocysteine, etc. Medical foods are manufactured according to FDA cGMP (current Good Manufacturing Practices). FDA actively enforces compliance with its medical foods regulations and performs regular inspections of medical foods manufacturing facilities. Unlike dietary supplements which are intended for healthy populations, medical foods are intended to meet the specific nutritional needs of a diseased patient population. Medical foods require physician supervision, and are required to be distributed by prescription in many states prior to reimbursement.

GRAS (Generally Recognized As Safe)

GRAS is a strict safety standard set forth by the FDA, requiring technical demonstration of non-toxicity and safety, as well as a general recognition and agreement by experts that the ingredients are safe for public consumption. Many ingredients have been determined by the FDA to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186. Other ingredients may achieve self-affirmed GRAS status via a panel of independent experts in the pertinent field who co-author a GRAS Report. Finally, a few ingredients have been specifically permitted by FDA as safe medical foods ingredients, e.g., Folic acid, in Volume 21 CFR Section 172.345(f). Some experts believe achieving GRAS status is an even higher standard of safety than the standard applied to drug products where a given compound is considered safe for a particular indication in a particular patient population at a particular dose for a specified duration of use, after a risk/benefit analysis. Dietary supplements, OTC drugs and prescription drugs are not required to have GRAS ingredients. Limbrel contains GRAS ingredients that have been safely consumed by widespread populations around the world.

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