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From conventional DMARDs to biologics in treatment of RA

The main goal in the fight against rheumatoid arthritis (RA) is to reduce inflammation and pain and to prevent or minimize joint damage. Due to an increased understanding of rheumatoid arthritis pathogenesis, the strategic plan in treating RA is to use disease modifying anti-rheumatic drugs (DMARDs) earlier and aggressively to alter the inflammatory process and slow down joint damage. Finally new biologics (biologic DMARDs) targeting T cells, B cells, and key inflammatory mediators can even stop inflammatory process and joint damage. Because most joint destruction with RA begins during the first two years of the disease, an early and aggressive treatment offers the best odds of stop its progression and preventing joint damage.

In the past decade, biologics such as monoclonal antibodies, cytokines, and others have extremely effective treated rheumatoid arthritis and other autoimmune diseases. A biologic is manufactured from a living cell, often plant or animal, and formulated to create a complex mixture of molecules. A traditional prescription drug is typically manufactured through chemical synthesis, which means that it is made by combining specific chemical ingredients in specific orders.

A traditional drug can be analyzed to determine all its various components. By contrast, it is difficult, if not impossible, to break down the components of a complex biologic. Biologics can be very sensitive to minor changes in the complex manufacturing process. Even small fluctuations in the process can significantly affect the final nature of the finished biologic drug and the way it works in the body. Each step of the manufacturing process must be carefully developed and monitored, and the final product need be verified through clinical trials.

Biologics are extremely expensive due to the intricacies of researching and developing suitable manufacturing processes and clinical trials. On average, it costs approximately $14,000 annually to treat one severe RA or lupus patient, and $ 27,000 annually for one Wegener's granulomatosis patient. Even factoring in the cost of research and development of biologic drugs, these medications provide pharmaceutical companies a financial windfall. Moreover, some pharmaceutical companies do an end-run around patent laws, avoiding competition by delaying generic alternatives to the marketplace. Therefore, in the foreseeable future, we will not have affordable biologics to treat severe RA and other diseases.

Today our country is at a crossroads in healthcare. We face unprecedented debt and unsustainable healthcare costs. Undoubtedly, biologics are very effective in treating in certain diseases. Yet, due to the cost, as well as safety issues, not all of these patients can be treated with biologics. Fortunately, many patients are still able to experience satisfactory response to appropriate conventional treatment. We must use biologics in a highly selective manner and balance the costs and benefits of this cutting edge treatment, reserving their use for those patients who really need it most.

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Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are widely prescribed to suppress the production of prostaglandins, a key chemical associated with inflammation. By decreasing prostaglandin production, the inflammatory substances that cause the pain, swelling, and redness commonly seen in arthritis can be reduced and controlled. On the other hand, not all prostaglandins are harmful, but offer beneficial elements to help protect the lining of our stomach.

Unfortunately, because NSAIDs and aspirin reduce the amount of "bad" prostaglandins to control inflammation, the effects of the "beneficial" prostaglandins are also reduced. This, in turn, creates a risk of gastrointestinal (GI) complications such as stomach irritation, ulcers, stomach bleeding, hypertension, water retention, even cardiovascular events with use of NSAIDs.

Although all NSAIDs operate in basically the same way, their actions are not identical. Not everyone responds the same way to a particular NSAID. One may be more effective for you and you may need to try different ones before finding the one that is right for you.

Patients on NSAID therapy, especially those with predisposing risk factors such as a history of ulcer, high dose NSAIDs, use of anti-coagulants or steroids, and being over seventy, are most commonly associated with NSAID induced ulcer complications and must be closely monitored because while most of these complications are quite noticeable, GI bleeding can occur without warning. Common symptoms include indigestion, nausea, vomiting, dizziness and black stools.

Acid suppressing therapies, such as proton pump inhibitors (PPIs) such as Prevacid, Protonix and Nexium, are vital pharmacological agents utilized for healing existing ulcers and for preventing recurrent ones. Combination NASID and PPI therapy such as Arthotec (diclofenac + misoprostol), Duexis (ibufrpfen+famotidine), Vimovo (naproxen+ esomeprazole), for arthritis has significantly deceased GI side effects.

Corticosteroid –Double Edges Weapon

Most inflammatory arthritis and autoimmune diseases were responsive to corticosteroids if they were given in an amount sufficient enough to cease the inflammation. Because of this immediate and powerful effect, it was considered a miracle drug. Since then, corticosteroids have been widely used to treat different diseases and many lives have been saved due to their powerful anti-inflammatory effect.

However, over the years, unpleasant side effects caused by corticosteroids emerged and became worrisome. The most common side effects were weight gain, high blood pressure, thinning of the bones, increased risk of becoming diabetic, increased risk of contracting an infection, poor sleep, cataracts, glaucoma, and abdominal stretch marks. Generally noted, the higher the dose of steroids and the longer they were prescribed, the greater the risk of side effects.

Low-dose corticosteroid treatment, particularly at the first 6-12 months, has been proved not only decreases inflammation and symptoms but slow down bone damage. Sometimes, long-term low-dose Prednisone (5mg to 7.5mg) therapy is appropriate for patients undergoing treatment for rheumatoid arthritis. During acute flare-ups, patients occasionally require a higher dose of Prednisone for a short period of time, which is decreased to the lowest effective dose or discontinued, if possible. Corticosteroids should be taken together with DMARDs to stop the progression of inflammation and joint damage.

Plaquenil and Minocycline for Mild Arthritis

Originally developed to treat malaria, Hydroxychloroquine (Plaquenil) has been used for many years to treat patients with mild rheumatoid arthritis that lack response to NSAIDs. While the exact reason for how Plaquenil works is not fully understood, it appears to interfere with our primate immune system, relieving pain and inflammation in about 30 % of patients. Since it has few side effects and does not require regular blood test monitoring, rheumatologists are willing to try it early in the course of mild rheumatoid arthritis (RA) and for patients with systemic lupus erythematous (SLE), especially those with skin and joint involvement.

Given orally, usually 200 mg twice daily or once daily as a maintenance dose, Plaquenil takes three to six months to take effect. Because its long-term benefits in treating RA are not as effective as that of other

drugs, Plaquenil can be taken in addition to Methotrexate (MTX) to achieve synergic effects to control severe rheumatoid arthritis.

Occasional side effects may include nausea or mild abdominal discomfort, a small possibility of skin rash and dizziness, and a very rare instance of retinal damage. As a general rule, Plaquenil is very safe if you take it under the supervision of your physician. A large number of my patients are taking Plaquenil with good results, but I do advise them to schedule yearly eye examinations, even the potential eye side effects are extremely rare. Minocycline, due to its anti-inflammatory effects, is also effective in patients with mild rheumatoid arthritis.

Methotrexate and Other DMARDs

Since the mid-1980s, MTX has become the more popular treatment for RA because of its effectiveness and ability to work more rapidly than other DMARDs. MTX is an anti-metabolite that interferes with the way cells utilize essential nutrients, which in this case is folic acid. In addition to its ability to inhibit the activity of our immune system and reduce inflammation associated with RA and psoriatic arthritis, MTX can also slow the growth of cancer cell when prescribed in a different dose, route and schedule. Therefore, the use of MTX in the treatment of RA cannot be regarded as a form of “chemotherapy".

Depending on the patient, MTX can be taken as a pill by mouth or as an injection. When taking the oral form, all the prescribed pills should be taken together, at the same time, or in two 12-hour intervals, on the same day, each week. For those who cannot tolerate the pill form due to gastrointestinal problems, MTX can also be given as weekly intramuscular injection.

Usually, MTX is started at 7.5 mg once a week, and gradually increased as needed, up to a maximum of 25 mg per week. Because it takes up to four weeks to take effect, NSAIDs (non-steroidal anti-inflammatory drugs) or corticosteroids are usually continued to control your symptoms. However, when the MTX kicks in, these medications may be decreased. Although MTX and NSAIDs may interact with each other, they can be taken together. Common side effects may include nausea, vomiting, loss of appetite, and mouth ulcers. However, these side effects can decrease and even disappear with usage. In order to reduce the incidence or severity of side effects, folic acid at 1mg daily except on the day you take MTX, can be very helpful. Patients on MTX may have mild thin hair, but almost never have major hair loss.

One important side effect that needs to be closely monitored is the very rare complication of liver damage. While taking MTX, liver functions should be monitored via blood tests, usually every two months, and it should not be taken while you are pregnant or breastfeeding. Furthermore, because alcohol and MTX both have the potential to affect your liver, it is advised that alcohol consumption be reduced or even eliminated.

Since DMARDs often take from several weeks to several months to work, trying them requires patience, commitment, and time. Once your symptoms have subsided, you may have to stay on DMARDs for a long period of time, though your doctor may try to decrease the dosage. While side effects can result from the use of DMARDs, severe ones are uncommon and are usually reversible once the drug is discontinued. Frequent laboratory monitoring will largely keep side effects from occurring.

Other DMARDs such as leflunomide (Arava), sulfasalazine (Azulfidine) have similar safety profile but not as effectiveness as MTX. Despite the powerfulness of DMARDs, only 50-60 percent of patients have satisfactory response to treatment. Even though they can slow down the progression of joint damage, the results are still unsatisfactory.

Combined two or even three DMARDs (MTX+ Azulfidine or MTX+ Azulfidine+Plaquenil) is also effectiveness for patients with inadequate response to MTX only. Some triple combined therapy studies showed similar effectiveness to biologic treatment. However, early discontinuation rate is high and compliance is low.

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Biologic DMARDs- Targeted Therapy

In the past few years, thanks to breakthroughs in genetic engineering, we have a better understanding of the role of T cells, B cells and chemical mediators in RA inflammation. Tumor necrosis factor-alpha (TNF), Interleukin-6 (IL-6), interleukin-1 (IL-1) and some other cytokines have proven to be the key chemical mediators which initiate, maintain and perpetuate inflammation and cause joint damage. The interaction of T cells and B cells also play a significant role in developing inflammatory cascade.

In 1974, W.Kohler and C. Milstein developed a process for generation of specific antibodies which can bind the target cells and chemical mediators. Since then, researchers are able to produce the desired antibodies (biologics) for specific therapeutic purpose. Like anti-missiles, they can lock in on a target and block the enemy's offensive maneuvers. Therefore, joint pain and damage can be impeded and even remission can be achieved in most patients. In the past decade, the treatment of rheumatoid arthritis and other autoimmune diseases enters the new era of biologic therapy.

A state of the art weapon called biologic agents which can effectively block major chemical mediators-TNF alpha, has been developed. Currently, there are five anti-TNF agents including etanercept (Enbrel), inflximab (Remicade), adalimumab (Humina), golimumab (Simponi), certolizumab pegol (Cimzia). Remicade and Simponi are administered by intravenous infusion. Enbrel, Humina and Cimza are administered subcutaneously. Simponi can be administered either subcutaneously or IV infusion. Anti-TNF agents can also be used to treat psoriatic arthritis, inflammatory bowel disease and ankylosing spondylitis. Tocilizumab (Acterama) is another anti-cytokine agent which inhibits IL-6 and is also used to treat RA. Anakinra (Kineret), blocking IL-1, is especially effective in the treatment of juvenile RA.

Other than anti-cytokine agents, there are two different biologic agents for the treatment of RA. Abatacept (Orencia) can relieve joint inflammation by inhibiting activation of T-cells. If T cells are not activated, inflammation cannot initiate. Orencia can be administered subcutaneously or IV infusion. Another biologic agent-rituximab (Rituxan) which targets and depletes B cells is administered IV infusion. Rituxan is also approved for Wegener's granulomatosis and microscopic polyangiitis.

Xeljanz (tofacitinib), a new oral DMARD was approved by FDA on November 6, 2012. JAKs are intracellular enzymes that regulate and transmit signals inside the cells. Xeljanz works by inhibiting the JAK pathway-a signaling pathway inside cells that play a significant role in inflammation associated with RA. Xeljanz is considered a small – molecule drug, not a biologic agent and can be used as mono therapy (alone) or combined with methotrexate or other non-biologic DMARDs. Xeljanz should not be used with biologic drugs or powerful immunosuppressant, such as azathioprine or cyclosporine.

Due to high cost and insurance restriction, anti-TNF agents are currently limited for patients with poor response or inadequate response to MTX or two different DMARDs such as methotrexate with plaquenil. In general, combination MTX and biologics is much effective than MTX or biologics alone.

Even though RA is a debilitating disease, these new drugs give us good reason to be optimistic. If it is treated early and properly, joint pain and swelling can be controlled and deformities can be prevented or minimized. Hopefully, soon, we will have the winning combination of fighting power to force RA into retreat and this "crippling arthritis" will become a thing of the past.

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