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How Biological and Non-Biological Disease Modifying Drugs are Used in the Treatment of Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis is a long-term disease that leads to chronic inflammation of the joints and the surrounding tissue. Effects of the inflammation are pain and destruction of the bone and cartilage, which leads to severe disability and, possibly, shorter life expectancy. That is why early diagnosis and aggressive treatment is a fundamental strategy to stop the progression of the disease and suppress the inflammation before the damage is irreversible.

In an attempt to avoid invasive treatments like arthroscopies and surgeries, the orthopedist's first choice of non-pharmacological treatments includes physical and occupation therapies. Pharmaceutical treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) and non-opioid analgesics (pain medication such as acetaminophen and aspirin) work on reducing the inflammation caused by rheumatoid arthritis, which often results in pain relief. Glucocorticoids, a class of steroid hormones, also possess anti-inflammatory effects and were once considered the most powerful treatment of inflammatory arthritis, but their use was virtually abandoned due to their association with toxicity; they are only used nowadays in controlling acute flare-ups joint disease. While these therapeutic strategies reduce inflammation and pain caused by rheumatoid arthritis, they are not that beneficial in slowing down the joint and bone damage and the progression of the disease. Rheumatologists didn't realize that while the pain was being covered by the medications and anti-inflammatory drugs, the inflammation and pannus (an abnormal layer of tissue) were continuing to cultivate inside the patients joints and articular tissue. For this reason, a new and very important group of agents called disease modifying anti-rheumatic drugs, or DMARDs, have become a major interest as a potential new therapy in the treatment of rheumatoid arthritis.

While most treatments focus on reducing the inflammation already present in the bone tissue and joints, DMARDs work on slowing down occurring bone damage and the progression of the disease by actually modifying the disease itself (Katzung 2001). They are different than other rheumatoid arthritis treatments because they work by suppressing the underlying factors that result in synovitis, tissue reactivity, erosions, ligament and tendon laxity, subluxations and other complications caused by rheumatoid arthritis (Johnson 2011). Since there is no presently known cure for rheumatoid arthritis, a lot of research is being done in finding a treatment that will stop or at least slow the progression of the bone damage caused by the disease, so that the patient can be in remission for a long period of time.

Discussion

Rheumatoid arthritis is an autoimmune disease that affects the synovia of joints and, eventually, the healthy surrounding tissue and bone, resulting in symmetric and erosive polyarthritis. According to Shah and Clair (2011), rheumatoid arthritis affects

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approximately 0.5-1% of the adult population worldwide. The ratio of rheumatoid-arthritis-affected women to rheumatoid-arthritis-affected men at premenopausal age is 4:1 while the same ratio at postmenopausal age is 1:1; this is attributed to the role that estrogen has in stimulating tumor necrosis factor-α, a major cytokine in the rheumatoid arthritis pathogenesis (Shah and Clair 2011). The exact etiology of rheumatoid arthritis is still unknown. It is known, however, that genetics plays some role in development and severity in certain patients. It remains a matter of debate whether the trigger of the disease is an exogenous infectious agent, a break in immune tolerance leading to classical autoimmunity, or simply random proceedings that accumulate with age (Klippel 2001).

While the auto-antigen that triggers rheumatoid arthritis has not been identified yet, the progression and evolution of the disease can be blamed on immune cells and mediators that contribute to the inflammation response that occurs. The process of how inflammation and erosion develop in synovial tissue and periarticular bone has been studied and researched in patients with rheumatoid arthritis. The primary agents involved in the immune response in rheumatoid arthritis patients are T-cells, which mainly function in stimulating other cells in the joint to produce and secrete cytokines. The most important cytokines involved in rheumatoid arthritis are tumor necrosis factor (TNF) and interleukin-1 (IL-1), both produced by macrophages and synovial lining cells that were activated by the T-cells in the joints. Once released, TNF and IL-1 stimulate the synovial cells to proliferate and produce factors contributing to the destruction of cartilage, such as inflammatory mediators and matrix metalloproteinases, which are endopeptidases. Eventually, bone destruction is caused by osteoclasts activated by a TNF ligand called RANKL (Receptor activator of nuclear factor kappa-B ligand), which is produced by T-cells and synovial fibroblasts. As the hyperplastic and hypertrophy synovium grows over the articular surface, pannus develops, which stimulates the resorption of surrounding cartilage (Kumar et al. 2005).

In addition to T-cells acting up, activated B-cells produce inflammatory-contributing autoantibodies. Some rheumatoid arthritis patients possessor develop rheumatoid factors, auto-antibodies that bind to the Fc fragment of Immunoglobulin G to form immune complexes that lead to the recruitment of polymorphonuclear leukocytes, further exacerbating the ongoing inflammation. The increasing pannus and inflamed synovium that spread over the articular cartilage produce large amounts of degradative enzymes (e.g. collagenase and stromelysin) that assist in irreversible cartilage destruction and subchondral bone erosion (Heaverstock and Jorizzo 2008).

Since it is a systemic disease, rheumatoid arthritis can affect internal organs as well, eventually leading to early death if left untreated. Rheumatoid arthritis typically affects joints of the hands and feet first, but can spring up in larger joints at any time. One of the essential factors of diagnosing rheumatoid arthritis is stiffness and soreness in the mornings after an extended lack of movement. Other clinical findings of rheumatoid arthritis are morning pain and swelling in areas such as the phalanges and on the balls of the feet. Routine morning activities, such as brushing ones teeth or hair, might become difficult due to the clinical manifestations. If left untreated, the disease will progress and result in increasing pain, swelling and stiffness caused by the destruction of the joints and healthy bones. Figure 1 shows irreversible bone and cartilage loss due to untreated rheumatoid arthritis.

DISEASE MODIFYING ANTI-RHEUMATOID DRUGS (DMARDS)

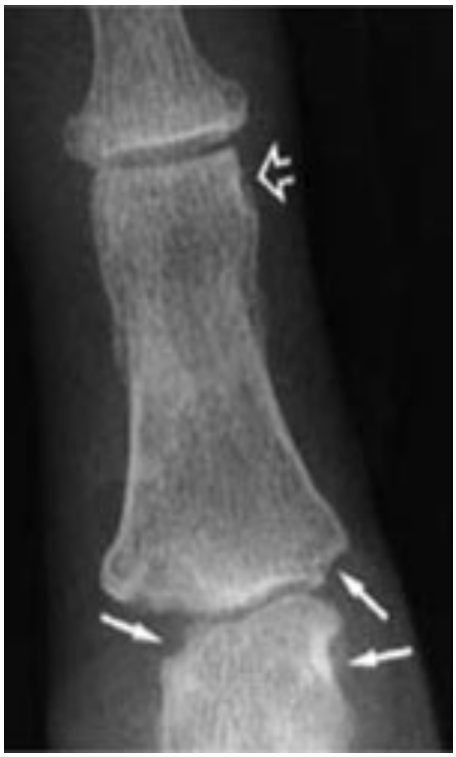

Figure 1:
Interphalangeal joint abnormalities. Osseous erosions are evident at the radial and ulnar aspects of the PIP joint of the second finger (arrows). Soft-tissue swelling and loss of interosseous space are additional findings. Marginal erosion is also seen on the middle phalanx at the distal interphalangeal joint (open arrow) . Source: Kountz and Von Feldt 2007

DMARDs are a class of drugs that include a diverse group of non-biological and biological agents. Although both work on suppressing the underlying cause of the inflammation in the disease, biological DMARDs are protein therapeutics that are designed mainly to target cytokines and cell-surface molecules that promote the inflammation response (Shah and Clair 2011). It may take 6 weeks to 6 months for the effects of the disease-modifying therapies to become evident since they are slow acting. It is necessary to start the use of DMARDs very early in the progression of the disease, since they work by slowing the progression and not reversing the damage already done. A large number of rheumatoid arthritis patients can reach remission or at least a low disease activity with the use of a single non-biological DMARD. However, for those patients with moderate or high disease activity or for those who failed to respond to a single agent due to prolonged disease duration, combinations of non-biological DMARDs are used.

Clinicians realized inadequate response was being achieved by patients being treated with monotherapy DMARDs, and a more aggressive treatment with DMARDs was essential for improving rheumatoid arthritis symptoms and slowing the progression of the disease. The use of biological DMARDs is reserved for those who indicate poor prognosis of the disease and do not respond to non-biological DMARDs treatment. Many patients who don't achieve sufficient results from either non-biological or biological DMARDS have treatment plans that include combining a synthetic DMARD with a biological DMARD in order to reach optimal responses from both agent types. DMARD agents are also commonly used in combination with non-steroidal anti-inflammatory drugs to reduce present inflammation and relieve pain.

Rheumatologists are trying to achieve early and sustained suppression of the disease activity with DMARDs. They believe that early detection of the disease and treatment with DMARDs might negate the need for NSAIDs and corticosteroids. Each rheumatoid arthritis patient's treatment is personalized, taking into account the severity of the disease and the potential adverse effects of the drugs. Since toxicity is a major concern with DMARDs, the effects of the drugs must be closely monitored, which can cost as much as the drug itself (Johnson 2011). Therefore, a large amount of effort and research is being put in to find the right combination of DMARDs that will work best on slowing the onset of the disease with reduction of the inconvenience of high costs and close monitoring. The latest research being done on the productivity and effectiveness of single, dual, and triple combination of synthetic DMARDs and biological DMARDs will be discussed in this paper, along with the safety monitoring that is necessary with the use of these drugs.

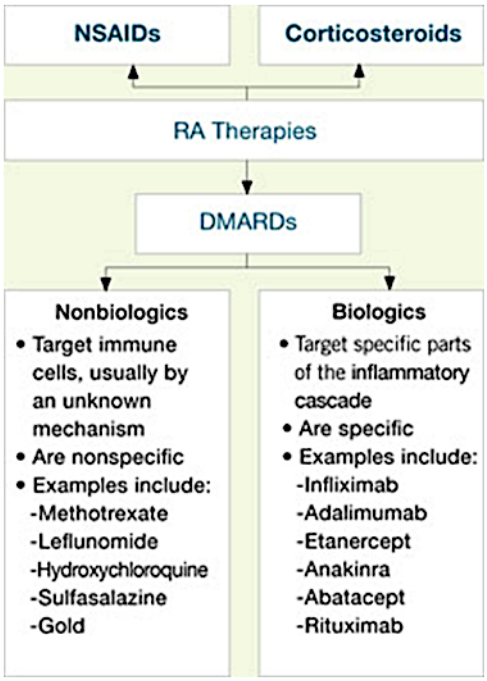

Figure 2: The three major rheumatoid arthritis therapies.
Source: http://stg.jfponline.com/ccp_article.asp?a=1&ref=5610ACCP_Supplement5#5610ACCP_Supplement5-fig7

It is important to understanding the mechanism of action of each individual drug, because DMARDs work by modifying the disease through inhibiting specific parts and pathways of the inflammatory response that occurs in rheumatoid arthritis. Knowing the mechanism also helps researchers decide which combination of drugs might work well together and which ones to experiment with, resulting in the finding of the most productive and effective treatment for the broadest variety of people.

COMMONLY USED SYNTHETIC DMARDS

Methotrexate, an analog of folic acid and of aminopterin, is the most commonly prescribed DMARD against rheumatoid arthritis in the United States and is usually the initial choice when using disease-modifying drugs in rheumatoid arthritis treatment. While its mechanism of action when used at a low dose in rheumatic diseases is unclear, it may relate to the polyglutamates metabolized from the methotrexate that cause extracellular adenosine to be released, which has anti-inflammatory and immunotherapy properties (Imboden et al. 2007). According to two meta-analyses, methotrexate has the best efficacy/toxicity ratio.

The most important action shown in studies of methotrexate against rheumatoid arthritis is its effects in increasing adenosine (anti-inflammatory agent) levels, lowering the pro-inflammatory cytokine levels, and increasing the anti-inflammatory cytokine levels (Swierkot and Szechinski 2006). Intensive treatment and observation while taking methotrexate is recommended in order to attain the most benefit from the drug. While patients tend to remain on methotrexate longer than any

other DMARD because of better clinical responses and less toxicity, a significant number of patients do not achieve premium control over the disease when taking the drug alone. As a result, methotrexate can either be used as a monotherapy or in combination with other synthetic DMARDs or anti-tumor necrosis factor agents, a class of biological DMARDs (Imboden et al.2007).

A study was done in Japan to evaluate the effectiveness of the government recommended 8mg/week dose of methotrexate given to people with rheumatoid arthritis. One hundred seventy-six patients with active rheumatoid arthritis at Konan Kakagowa Hospital and Kobe University Hospital participated in the study. The effects of methotrexate were evaluated by the American College of Rheumatology (ACR) core set, which showed maintained improvements in the clinical signs and symptoms of rheumatoid arthritis for 24 months. However, according to European League Against Rheumatism (EULAR) response criteria, 63.5% of the patients were found nonresponsive at 24 months from the methotrexate therapy. Despite the treatment, x-rays showed the progression of joint destruction. This study is important because it verifies as mentioned before that many patients do not achieve sufficient disease control when using methotrexate as a monotherapy (Hashiramoto et al. 2009). Most combination therapies involve using another DMARD with methotrexate, to enhance the methotrexate clinical response.

Leflunomide is another very important synthetic DMARD that is widely used. Once administered, leflunomide is well absorbed and quickly metabolized in vivo into A771726, which is the active form of the drug. At its molecular level, leflunomide is a pyrimidine synthesis inhibitor that inhibits dihydroorotatedehydrogenase, an enzyme involved in the synthesis of pyrimidines. Unlike other cells during proliferation, lymphocytes increase their pool of pyrimidines much more than their increase in purines, therefore synthesizing them from both salvage and de novo pathways. By inhibiting dihydoorotatedehydrogenase, A771726 prevents the damaging lymphocytes from accumulating enough pyrimidines to support DNA synthesis, which is why leflunomide is considered an immunosuppressive agent.

In addition to being a pyrimidine synthesis inhibitor, current research is being done to investigate A771726's effect on inhibiting the over-expression ofCD147, thereby resulting in the down-regulation of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) in active macrophages. CD147 is a member of the immunoglobulin superfamily, which consists of autoantibodies that are linked to autoimmune diseases such as rheumatoid arthritis. Pro-inflammatory cytokines, such as TNF, interleukin 1 and interleukin 17 are released in patients with rheumatoid arthritis and work synergistically to release matrix metalloproteinase-3's (MMP3) from fibroblast-like synoviocytes and macrophages. MMP3's are connected to pathologic tissue destruction, making them a vital interest to the research being done to find a cure for rheumatoid arthritis.

Since CD147 is known to induce several MMP3's and its expression levels have been found elevated in the synovial membranes of rheumatoid arthritis patients, research is being done that focuses on CD147 as a novel target in the treatment of rheumatoid arthritis. A study was done on phorbol myristate acetate differentiated THP-1 cells line, a monocyte-macrophage, to observe the effects of leflunomide's active metabolite on CD147 levels. As MMP3's are the major MMPs secreted by activated inflammatory macrophages and markers of progression of joint damage in

early rheumatoid arthritis, the effects of A771726 on MMP3 gelatinases were also evaluated in this study.

In the macrophage cell model used in the study, an increased mRNA expression of MMP-2 and MMP-9 (both of which can be activated by MMP3) occurred in addition to the up-regulation of CD147, once the cells differentiated. The results found in the study showed that A771726 did not affect the mRNA expression of CD147, but did inhibit CD147 protein expression on the cell surface in a dosage dependent manner, which demonstrates that A771726 only has post-transcriptional effect on CD147 production in THP-1 cells. The authors go on to suggest that future studies should be conducted on the effect of A771726 on the glycosylation of CD147, since abnormal glycosylation was the cause of the instability of the CD147 proteins in their experiment. The study also showed that A771726 inhibited the induced increase of gelatinolytic activity of MMP-2 and MMP-9. The authors conclude by saying that their study indicates that A771726 inhibits the production of CD147 and the gelatinolytic activity of MMP-2 and MMP-9 in THP-1 cells, and they suggest that serum concentration of the metabolite should be monitored in rheumatoid arthritis patients so that sufficient concentration is maintained to allow the patient to achieve remission (Juang et al. 2011).

Leflunomide can also be given as a combo-therapy. The thought of combining leflunomide with methotrexate as a double combination therapy was inspired by the idea that combining methotrexate with an agent whose mechanism of action was different than its own might produce better results than methotrexate monotherapy. In 1999, a study was done on the safety and efficacy of treating active rheumatoid arthritis with a combination treatment of methotrexate and leflunomide. It was a 52-week open-label study in which 30 patients who had active rheumatoid arthritis despite previous methotrexate treatment participated. Adverse effects and clinical response, as judged by the American College of Rheumatology 20% response criteria, were assessed as end point results. Of the patients, 53% met the ACR 20% response criteria and 2 patients met the ACR remission criteria after 1 year. While the study was only done on 30 patients and only a little more than half the patients met the ACR criteria, the study did introduce methotrexate and leflunomide combination therapy as a potential rheumatoid arthritis treatment (Mroczkowski et al. 1999).

In 2004, another study was done on the safety and efficacy of the combination therapy of leflunomide with methotrexate. After a 24-week, randomized, double blind trial of taking leflunomide or a placebo with methotrexate, the patients could enter a 24-week extension to continue the study. Results showed a 48-week maintained response to therapy for those patients who continued to receive leflunomide plus methotrexate. ACR 20% responder rates improved in the patients who switched from taking placebos to leflunomide. Similar ACR 20% response rates were found between patients who switched from placebo to leflunomide without a loading dose to those who received a randomized loading dose of leflunomide. However, fewer adverse events of diarrhea and nausea were found in those who did not receive the extra dose. In addition, patients who switched from placebo to leflunomide in the extension exhibited a lower incidence of elevated transaminases compared to the patients who were initially taking leflunomide throughout the 48-week trial, which may indicate possible hepatotoxicity caused by leflunomide (Kremer et al. 2004). While leflunomide might slow the progression of the disease, patients must discuss with their doctors

required monitoring and possible combination therapies that will yield the best efficacy/toxicity ratio while taking leflunomide.

Besides for leflunomide and methotrexate, there are other synthetic DMARDs used to treat rheumatoid arthritis. Both sulfasalazine and hydroxychloroquine were initially developed for other disease like inflammatory bowel disease and malaria, but they were coincidentally found to be effective in rheumatoid arthritis. They are weak DMARDs, which is why they are usually only used as monotherapy in the early stages of rheumatoid arthritis or used in combination with other DMARDs such as methotrexate. With the use of hydroxychloroquine, ophthalmologic examinations are required every six to twelve months to detect color change or evidence of drug in the retina. Sulfasalazine, the most common used DMARD in Europe, is usually combined with methotrexate, hydroxychloroquine, or both. It is recommended that blood cell counts, especially white blood cell counts, be monitored in the first six months of taking sulfasalazine.

Required monitoring while taking these drugs is evidence of how expensive and time-consuming DMARD treatments can be. This is why such an abundant amount of research is being done to find the most effective and convenient DMARD treatment against the autoimmune disease.

A study was done to compare the efficacy of double or triple combination therapies involving methotrexate, sulfasalazine and hydroxychloroquine in patients with rheumatoid arthritis. Combinations of the different therapies were either methotrexate (MTX) with hydroxychloroquine (HCQ), MTX with sulfasalazine (SSZ), or the triple combination of MTX, HCQ and SSZ. One hundred seventy-one rheumatoid arthritis patients who were not previously treated with the medications were randomized to receive one of the three treatment combinations in this 2-year, double blind, and placebo controlled trial. The end point goal was to find the percentage of patients after 2 years who had a 20% response to their assigned therapy according to the American College of Rheumatology. While all combination treatments were well-tolerated, patients receiving the triple treatment responded best with 78% of them achieving the 20% ACR response required, compared to the 60% percent of those receiving MTX and HCQ and only 49% of those receiving MTX and SSZ (O'Dell et al. 2002).

Commonly used biological DMARDs

Pro-inflammatory cytokines, especially tumor necrosis factor-α and interleukin-1, have vital roles in the pathophysiology of rheumatoid arthritis. This fact led to the development of biological agents that target TNF-α and interleukin-1 cytokines. In addition, recent research has been done that shows promise for therapies that block T-cell co-stimulation and those that target B-cells. Since biological disease modifying anti-rheumatoid drugs have only recently been studied, and possible long-term adverse effects are still unknown, they are usually saved for use in combination therapies with other DMARDs such as methotrexate and leflunomide, for those rheumatoid arthritis patients who did not respond to synthetic DMARD monotherapy.

DMARDs that are anti TNF-α agents include etanercept, infliximab, and adalimumab. Etanercept, a protein genetically engineered from a fusion gene, consists of two soluble TNF p75 receptor functional groups linked to the F_c portion of human

immunoglobulin-1. It binds to TNF-α molecules, thereby preventing the activation of the inflammatory cascade, in addition to inhibiting lymphotoxin-α (O'Dell 2007).

A study was done on the efficacy of etanercept combination therapy with methotrexate, where 89 patients previously treated with methotrexate, who still showed signs of active rheumatoid arthritis symptoms, were randomly assigned to receive either etanercept or placebo subcutaneously, while continuing methotrexate therapy. At 24 weeks ACR response criteria was used to measure clinical response in improvements. Results showed that at 24 weeks 71% of the patients receiving etanercept-MTX combination therapy met the ACR 20% response criteria, compared to 27% of the group receiving placebo plus MTX. Thirty-nine percent of the etanercept group reached ACR 50% response criteria compared to the 3% of the placebo group. Significantly better outcomes, according to all measures of disease activity, were present in the patients receiving the etanercept-MTX combination therapy. Adverse effects associated with etanercept in this trial included only mild injection-site reactions, showing etanercept as a safe and potential combination therapy in patients with active rheumatoid arthritis who didn't respond sufficiently enough to methotrexate therapy alone (Weinblatt et al. 1999).

Infliximab is a 25% mouse and 75% human monoclonal antibody that bind to soluble and membrane bound TNF-α cytokines with high affinity, preventing them from interacting with their receptors, resulting in the down-regulation of macrophage and T cell function.

Adalimumab is a recombinant human anti-TNF antibody. By combining with TNF-α, it prevents its interaction with its p77 and p75 cell surface receptors, resulting in the down-regulation of macrophage and T-cell function, which is similar to infliximab's mechanism of action (Furst et al. 2009). A 24-week, randomized, double-blind, placebo-controlled study was done in 2002 to test the efficacy and safety of adalimumab in combination with MTX given to patients with active rheumatoid arthritis who have not responded adequately to previous MTX mono treatment. The results showed that an ACR 20%, 50% and 70% response were all achieved by a significantly greater proportion of patients in the adalimumab plus MTX administered group than in the groups given placebos with MTX. The greater the dose of adalimumab was given, increasing from 20-mg to 40-mg, to 80-mg, respectively, the higher the response rate appeared. Response seemed rapid, as the greatest proportion of adalimumab-treated patients achieving an ACR 20% response occurred at the first scheduled visit of one week. Adverse events were similar in both control groups, indicating that adalimumab was well tolerated (Weinblatt et al. 2003).

While this clinical trial did demonstrate that adalimumab with combined MTX therapy has been effective in reducing signs and symptoms of active rheumatoid arthritis, and does give hope for potential combination therapy, the study was only held for 24 weeks. While this might be sufficient to show improvements caused by adalimumab in rheumatoid arthritis symptoms, it does not show how effective adalimumab is in the long run at stopping the progression of the disease, or pushing the patient into remission (Kremer et al. 2008).

Abatacept, a recombinant protein, acts by blocking T-cell co-stimulation and preventing the autoimmune response caused by rheumatoid arthritis. A study was done on 652 patients who had active rheumatoid arthritis, despite previously being

treated with methotrexate, to see the efficacy of abatacept. 433 patients were randomly assigned to be given an infusion of a fixed dose of abatacept once a month, while 219 received placebos. Results showed at one year, progression of structural joint damage was statistically slowed by abatacept. Physical function significantly improved in 63.7% of the patients. While these results seem to be very promising for abatacept therapy, the study only involved 1 group of patients over 1 year and therefore is very limited in its evidence of the efficacy of the drug. Longer treatment in different populations is needed to establish its effectiveness against the progression of rheumatoid arthritis (Kremer et al. 2008).

Rituximab is a genetically engineered humanized mouse monoclonal antibody that works against CD20 molecules on the B-cell surfaces, thereby depleting the B-cells, stopping their immune response and thereby reducing inflammation (Furst et al. 2009). The advantage of rituximab is that it works on B-cells rather than inhibiting TNF cytokines, which is a relief to patients who do not benefit from anti-TNF agents, either at the start of treatment or after receiving some treatment. A study was done in Finland to examine the effectiveness of rituximab on rheumatoid arthritis patients who failed to respond to TNF antagonists, or had a contraindication to these drugs. Data was collected from five rheumatology clinics and examined 81 patients in total who were treated with rituximab from April 2005 to June 2008, since previous therapies were unsuccessful in reaching adequate responses. Treatment response was defined according to EULAR response criteria and disease activity score using 28 joint counts (DAS28). The results of the trial showed adequate EULAR response in 77% of the patients and a suppressed DAS28 score of 2.08 units. Since the percentage of good responses of patients taking DMARDs other than methotrexate with rituximab, was somewhat higher than those taking methotrexate alone with rituximab, it's obvious that rituximab is equally effective when combined with methotrexate and other DMARDs. The study concludes that rituximab was effective in controlling disease activity in patients who did not show adequate results taking other DMARDs alone (Valleala et al. 2009).

Tocilizumab is the first of its kind as an anti-interleukin 6 receptor monoclonal antibody. Interleukin 6, a pro-inflammatory cytokine that is released by immune, endothelial and synovial cells, induces osteoclast differentiation, therefore contributing to the joint and bone destruction occurring in rheumatoid arthritis patients. The drug is typically given with or without methotrexate, for patients who did not respond to single or multiple anti-TNF therapies. Similarly to those associated with other monoclonal immune suppressors, adverse effects include infusion reactions, development of neutralizing antibodies, hypersensitivity reactions, and increased risk of serious infection (Murri 2010).

Studies done on rheumatoid arthritis patients who took tocilizumab with methotrexate revealed positive results. One study was done on 499 patients who had an inadequate response to one or more anti-TNF agents. Results after the 24 weeks showed that 50.0% of those who received 8mg of tocilizumab achieved ACR 20% response criteria, compared to the 30.4% in the 4mg group and the 10.1% in the placebo group. At week four, ACR 20% response criteria was reached by more patients receiving 8mg of tocilizumab than those in the control groups, as was DAS28 remission rates achieved at week 24. The most common adverse events reported in the trial were infections, gastrointestinal symptoms, rash and headaches; however, most

were mild and moderate. This study demonstrates the potential benefit of tocilizumab given with methotrexate as an effective therapy against rheumatoid arthritis (Emery et al 2008). Results showed rapid and sustained improvements of rheumatoid arthritis symptoms for those who failed to respond well to TNF antagonists and reported mild adverse effects.

Even though the biological DMARDs mentioned above did show promising trial results when given with methotrexate, biological DMARDs are so fresh and new in research that efficacy and adverse effects are unable to be studied in the long run. Most of these trials are over a 1 to 2 year period, which is not an adequate amount of time to measure achievable long-term remission induced by these therapies. While they definitely show great potential in slowing down the progression of bone destruction and active symptoms caused by rheumatoid arthritis, more research and long-term studies must be done to evaluate the lasting effects and possible negative side effects of these young progressing therapies.

ADVERSE EFFECTS AND DISADVANTAGES

Potential increased risk of serious infection is one of the major side effects of biological DMARDs. TNF inhibitors in particular have been noticed to increase the risk of developing reactivation of dormant tuberculosis. This is why it is important for a patient who is about to start on anti-TNF agents to undergo tuberculin skin testing and even chest radiographs, if needed. A national prospective observational study was done on data collected from the British Society for Rheumatology Biologics Register (BSRBR) to test if different anti-TNF agents increase the risk of tuberculosis reactivity. A comparison of TB rates in 10712 patients who were either treated with etanercept, infliximab, or adalimumab showed three-to four-fold higher TB rates in patients taking infliximab and adalimumab, than those receiving etanercept (Dixon et al. 2010).

Another prospective observational study was done from the BSRBR, where 11,881 patients treated with anti-TNF agents were evaluated to research an increased risk of septic arthritis. While the results did not show that anti-TNF therapy was a significant cause of Septic Arthritis, they did find that it was associated with doubling the risk of developing SA.

Both studies were done on an enormous number of subjects who might have had different contributing factors in developing tuberculosis or septic arthritis (Galloway et al. 2011). While these studies do not positively prove that anti-TNF agents used in rheumatoid arthritis patients increase the risk of infection and tuberculosis, they do show a probable basis for the fact that TNF inhibitors might contribute to these risks. For this reason, physicians and surgeons should be aware of these potentially life-threatening complications, and instruct their patients on how to manage and prevent these adverse outcomes.

The cost of DMARDs and the necessary monitoring required while being treated with these drugs can be extremely expensive and burdensome, especially for elderly patients with severe rheumatoid arthritis. A large amount of monitoring is needed while on DMARD treatment, since complications such as infection and toxicity can occur. Tests such as CBCs and platelet counts are necessary periodically to rule out infection, and yearly ophthalmologic tests are needed for patients on

hydroxychloroquine. All in all, sometimes the excessive expense and adverse effects might prevent patients from benefiting from these new and promising treatments.

CONCLUSION

Rheumatoid arthritis can be a crippling and incapacitating disease, if left untreated. Disease modifying anti-rheumatic drugs work in the unconventional way of modifying the disease and inhibiting the underlying cause of inflammation present in rheumatoid arthritis, in order to reach sustainable remission. While it is a relatively new group of drugs, an abundant amount of research and effort has been put in to find the most suitable and effective treatment when using these agents. From the studies mentioned above, it is obvious that DMARDs has a tremendous potential of becoming the leading treatment in autoimmune inflammatory disease, such as rheumatoid arthritis. According to Tak et al. (2011), the complex and varied mechanism of actions of these drugs make it necessary for researchers to study the different mechanism and contemplate which combinations are effective and safe. What's more, rheumatologists should put effort in predicting clinical responses of individual patients who they prescribe DMARDs to. By doing so, the physician may very possibly maximize the patient's outcome, minimize safety concerns and reduce treatment costs caused by complications (Tak et al. 2011). Even though there is a long way to go, DMARDs are thriving at helping people overcome rheumatoid arthritis, and show great potential in some day reaching the ultimate goal of causing rheumatoid arthritis patients to go into permanent remission, thus becoming the cure for rheumatoid arthritis.

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