

Remission

as a goal of inflammatory arthritis treatment

Until recently, the idea that remission could be a goal of treatment seemed unrealistic and impossible for many of us living with inflammatory arthritis. However, that has changed.

Recent advances in science have led to a better understanding of how inflammatory arthritis progresses in the body, and how the most common forms of it are most effectively treated. This knowledge has contributed to the development of new therapies for inflammatory arthritis and innovative approaches to treating the disease. Gone are the days of the "go slow" treatment regimen. Today, it is widely accepted that treatment, particularly for inflammatory arthritis should be started early and aggressively to stop the progression of the

In this issue of JointHealth monthly, we look at remission as a goal of arthritis treatment, making medication decisions, and new medications being developed for use in arthritis treatment.

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disease in order to prevent joint damage and increase chances of remission.

Research shows that different medications, and combinations of medications, increase the chances of achieving remission. For example, patients with rheumatoid arthritis who are

treated with a single conventional disease modifying anti-rheumatic drugs (DMARDs) have lower chances of achieving remission than do patients who are on combination DMARD therapy or a combination of methotrexate with a biologic response modifier.

In addition to medications, other factors have been associated with increased chance of remission including: older age, lower body mass index, being a non-smoker, having a shorter duration of symptoms and a low erythrocyte sedimentation rate (ESR - a measure taken of the blood to determine a person's level of active inflammation). A recent study also found that women were less likely to be in remission than men; 17% and 30% respectively.

What is remission?

Remission is defined as the "nearly complete suppression of the inflammatory process or absence of evidence of disease activity".

While there are differences in the established criteria for defining remission, the American College of Rheumatology (ACR), the United States Federal Drug Agency (FDA) and the European League Against Rheumatism (EULAR), have very similar components including:

- No joint pain
- Morning stiffness of less than 15 minutes
- ESR (Erythrocyte Sedimentation Rate) of less than 30 mm in women or less than 20 mm in men

- Normal CRP (C-Reactive Protein)
- No joint or tendon-sheath swelling
- No joint tenderness
- Some also include combination measurements such as the Disease Activity Score (DAS), the DAS 28 and others.

In addition to these criteria, imaging techniques such as X-Ray, MRI and CT scans, are also increasingly used to determine if a patient is in remission. The use of these tools seems particularly important as research shows that even if a patient has met all the criteria for remission, the disease may continue to smolder, doing structural damage to the joints.

Achieving remission: treating the underlying disease process

Remission is, for the most part, a product of the right treatment at the right time for the right patient. A key aspect of an effective treatment regimen is addressing the underlying disease. As forms of inflammatory arthritis, such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, are autoimmune diseases, gold-standard treatments target specific aspects of the disease process.

Disease modifying anti-rheumatic drugs (“DMARDs”)

These drugs are slower acting, typically taking about 3 months – sometimes longer – to take effect. They include:

- methotrexate (most commonly used)
- hydroxychloroquine (Plaquenil®)
- sulfasalazine (Azulfidine®)
- leflunomide (Arava®)
- azathioprine (Imuran®)

For most types of inflammatory arthritis, DMARDs remain the choice of conventional first line therapy. However, research shows that when DMARDs are used alone, remission rates are low with less and one-fourth of patients achieving remission.

For that reason, today, patients are often started on a combination of DMARDs as soon as they are diagnosed. This helps to increase a patient’s chance of achieving remission. Studies have shown that remission rates for patients taking a combination of DMARDs ranges from 10% -65%, being highest when the treatment regimen is closely monitored and adjusted in order to achieve a low level of disease activity.

However, if a patient fails on a number of DMARDs (as well as combinations of DMARDs) and still has uncontrolled disease, a biologic response modifier may be recommended.

Biologic DMARDs (“biologics”)

These are the newest class of medications used for treating the most common forms of inflammatory arthritis. Biologics provide faster-acting (2-12 weeks) and targeted action against specific aspects of the disease process, with patients being able to notice the effectiveness of the drug within approximately 3 months of starting. Some experience a dramatic benefit within days or a few weeks.

Currently, there are 6 biologic medications available in Canada for treating various forms of inflammatory arthritis. These include:

- **abatacept (Orencia®)**

This is one of the newer biologics. This

medication is a “selective co-stimulation modulator” that targets t-cells. It works by blocking the activation of T-cells, making them inactive. This is important as T-cells are a specific type of immune cell found in the joints of persons with inflammatory arthritis that cause inflammation and subsequent joint damage. This medication is given by an initial intravenous infusion the first week, then another at weeks 2 and 4, then every four weeks thereafter. This 30 minute infusion can be given by a nurse at home.

- **adalimumab (Humira®)**

This is an anti-TNF medication. It works by blocking the tumour necrosis factor (TNF) cytokine, which causes inflammation. In doing so, this medication helps to reduce pain and disease progression. This medication is taken by one injection every two weeks.

- **anakinra (Kineret®)**

This medication targets IL-1, which is a cytokine that promotes inflammation. It works by blocking IL-1, reducing the inflammation, pain, and progression of disease. This medication is taken daily by injection.

- **etanercept (Enbrel®)**

This is an anti-TNF medication. It blocks the production of the tumor necrosis factor (TNF) cytokine, which causes inflammation. Blocking TNF reduces inflammation, pain, and disease progression. This medication is taken by injection once a week.

- **infliximab (Remicade®)**

This is an anti-TNF medication. It blocks the production of the tumor necrosis factor (TNF) cytokine, which causes inflammation. Blocking TNF reduces inflammation, pain, and disease progression. This medication is taken by intravenous infusion, every 2 months, always given with methotrexate. This infusion lasts a couple of hours and will be given in a clinic or hospital.

- **rituximab (Rituxan®)**

This is also one of the newer biologics. This medication works by targeting and reducing a specific type of immune cell found in the body, called B cells. These are important targets for treatment because B cells play a key role in the immune system. Although scientists do not fully understand how the medication works in the body, the result is a prolonged decrease in inflammation. This medication is taken through intravenous once, then again 2 weeks later, and then approximately 9 months later. This infusion is several hours in duration and is given in a hospital or clinic.

Research shows that the use of biologics, in combination with a DMARD (often methotrexate) increases the chances of achieving remission. For example, studies have shown that patients taking methotrexate and an anti-TNF medication had remission rates between 21% -49%.

While existing medications provide critical value for patients living with inflammatory arthritis, we also know that there continues to be a significant unmet need for new treatments. Research shows that:

- 28-58% of patients with rheumatoid arthritis do not respond to anti-TNF drugs
- Patients with rheumatoid arthritis also experience issues of drug resistance with anti-TNF therapy over time.
- Almost 60% of people with rheumatoid arthritis who have tried one or several of the biologics on the market have not responded well (or responded well enough).
- In other words, more than half of people with inflammatory arthritis do not have their symptoms alleviated with the current biologics.

It is important that patients and their health care providers have access to a broad range of medications. Through research we know that the disease involves a number of different molecules that cause or promote inflammation - the one symptom that is so devastating and damaging in inflammatory arthritis.

This means that two people living with rheumatoid arthritis may have different responses to the same cocktail of medications. So while it is useful for a person with rheumatoid arthritis to ‘compare notes’ with other people with rheumatoid arthritis, one should not expect the same response to the medications.

Risks and side effects

All medications, including those used to treat arthritis, come with some risks and side effects. While there are variations between the drugs, common side effects and risks of DMARDs may include: headache, stomach upset, increased risk of infection, skin rash, diarrhea and nausea. For biologics, common side effects and risks may include: injection or infusion site reactions, headache, dizziness, possible increased risk of lymphoma, increased risk of serious infection, vision changes and others.

For more information on medications and provincial/territorial drug reimbursement formularies see: http://www.jointhehealth.org/pdfs/MedicationChart_E_web.pdf

Making decisions about treatment:

is switching from one biologic medication to another effective?

Living with inflammatory arthritis means having to make many decisions about treatment. Increasingly, one of those decisions centers on switching from one biologic medication to another, either because of treatment failure, or as part of the journey to discovering which treatment cocktail works best.

As well, governments and private insurance payers often need to make decisions about criteria for medication reimbursement coverage. These criteria frequently put forward an order in which biologics must be tried to qualify for reimbursement. Some provincial pharmacare

programs have required that two anti-TNF medications be tried and failed by a patient before another biologic is tried.

As provincial pharmacare programs and private insurance plans vary widely, it is useful to examine the evidence around retrying anti-TNF biologics when a patient has already failed one.

- For people with rheumatoid arthritis, first time use of anti-TNF medications is quite effective. Research has shown us that 42% patients achieve good response and 33% have a moderate response to first time anti-TNF therapy

- However, switching from one anti-TNF medication to another anti-TNF medication is generally less effective. For example, one study showed that only 20% achieved good response, 27% of patients achieved moderate response and 53% of patients had no response to a second trial of anti-TNF medication
- Research shows that if patients discontinued the first anti-TNF medication because of an adverse effect and then switched to another anti-TNF, an even higher percentage of patients would stop taking the drug because of adverse events

New treatment targets in the pipeline

There are a range of new medications under development for the treatment of rheumatoid arthritis and other forms of inflammatory arthritis, such as psoriatic arthritis, ankylosing spondylitis and lupus. Some of these medications have similar molecular targets to the drugs currently available, while other drugs under study focus on new targets, or aspects of the disease. All of these medications are in varying stages of development. Some have recently received approval from the Food and Drug Administration (FDA) in the U.S., while others are in Phase II and Phase III clinical trials.

Anti-TNF medications

Tumor necrosis factor (TNF) is a cytokine (protein) that promotes inflammation in the body, which contributes to pain and disease progression.

- **golimumab (CNTO 148®)**

This is an anti-TNF medication. It is taken by subcutaneous injection every 4 weeks. Currently, it has been submitted for approval to the FDA in the U.S. and is under review.

- **certolizumab (Cimzia®)**

This is an anti-TNF medication. It is taken by subcutaneous injection at a dose of 200-400mg every two weeks after a loading dose of 400mg twice. Currently, it is in Phase III clinical trials for the treatment of rheumatoid arthritis.

Interleukin drugs

Interleukins are a group of cytokines that pass information between the cells, playing an important role in immune function and

inflammation in the body. While there are many types of interleukins, two in particular have shown to be important targets in the development of medications for the treatment of forms of inflammatory arthritis such as rheumatoid arthritis, psoriatic arthritis and lupus: interleukin 6 (IL-6) and interleukin 15 (IL-15).

- **tocilizumab (Actemra®)**

This drug targets interleukin-6 (IL-6), which is a cytokine that is over-produced in the joints of patients with rheumatoid arthritis,



contributing to inflammation, swelling, joint damage and possibly other issues such as anemia and platelet elevation. It works by blocking the effects of IL-6. It is taken by intravenous infusion every 4 weeks. This medication was recommended for approval in the United States by the Arthritis Advisory Committee of the FDA; however, the FDA has requested further information and approval is still pending. In Canada, it is currently under review for rheumatoid arthritis.

B cell drugs (anti CD20)

Through research, we now know that b cells

play an influential role in inflammatory arthritis including rheumatoid arthritis and systemic lupus erythematosus, by releasing pro-inflammatory cytokines (including tumour necrosis factor- α), which creates rheumatoid factor and other autoantibodies, and activating T cells. Two new medications under study are:

- **ocrelizumab:** This medication is in Phase III clinical trials for the treatment of rheumatoid arthritis and lupus nephritis.

- **ofatumumab (HuMax-CD20):** This medication is in Phase III clinical trials for the treatment of rheumatoid arthritis.

Other medication targets

- **RANK ligand:** Is a protein that contributes to the development of bony erosions, which are one of the key features of RA disease. Currently it is under study for the treatment of rheumatoid arthritis and osteoporosis.
- **Small molecules:** kinase inhibitors are one target as they play an important role in signaling aspects of your body's immune response.
- **Gene profiling:** this would help to better predict how a person will respond to a medication so that a rheumatologist could more effectively tailor treatment that best suits a patient's genetic makeup.

In addition to new targets, many of the biologics currently available to treat rheumatoid arthritis are under study for other types of inflammatory arthritis such as lupus, ankylosing spondylitis and juvenile idiopathic arthritis. For more information on clinical trials see <http://clinicaltrials.gov/>

Arthritis Consumer Experts

Who we are

Arthritis Consumer Experts (ACE) provides research-based education, advocacy training, advocacy leadership and information to Canadians with arthritis. We help empower people living with all forms of arthritis to take control of their disease and to take action in health care and research decision making. ACE activities are guided by its members and led by people with arthritis, leading medical professionals and the ACE Advisory Board. To learn more about ACE, visit

www.jointhehealth.org

Guiding principles and acknowledgement

Guiding Principles

Health care is a human right. Those in health care, especially those who stand to gain from the ill health of others, have a moral responsibility to examine what they do, its long-term consequences and to ensure that all may benefit. The support of this should be shared by government, citizens, and non-profit and for-profit organizations. This is not only equitable, but is the best means to balance the

influence of any specific constituency and a practical necessity. Any profit from our activities is re-invested in our core programs for Canadians with arthritis.

To completely insulate the agenda, the activities and the judgments of our organization from those of organizations supporting our work, we put forth our abiding principles:

- ACE only requests unrestricted grants from private and public organizations to support its core program.
- ACE employees do not receive equity interest or personal "in-kind" support of any kind from any health-related organization.
- ACE discloses all funding sources in all its activities.
- ACE identifies the source of all materials or documents used.
- ACE develops positions on health policy, products or services in collaboration with arthritis consumers, the academic community and health care providers and government free from concern or constraint of other organizations.
- ACE employees do not engage in any personal social activities with supporters.
- ACE does not promote any "brand", product or program on any of its materials or its web site, or during any of its educational programs or activities.

Thanks

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