Lifelong Learning

Biological Therapies for Rheumatoid Arthritis: Non-TNF Inhibitors

Non-tumour necrosis factor (non-TNF) inhibitors are highly effective biological therapies that have radically changed how rheumatoid arthritis is managed, helping patients achieve not only disease control but long-term remission.

Therapy for rheumatoid arthritis (RA) is directed at interrupting the inflammatory process, which, if left unchecked, causes irreversible joint damage, deformity and long-term functional impairment. The earlier therapy is initiated, the better the long-term outcomes in patients with RA. Methotrexate is the main disease-modifying anti-rheumatic drug (DMARD) used for the treatment of RA and remains the gold standard of first-line therapy. However, an emerging class of biological DMARDs is now available for patients who fail to respond to methotrexate monotherapy and/or combination therapy with other traditional DMARDs. Treatment with these new biological DMARDs is designed to specifically target the immune response underlying the development and progression of RA.

The non-TNF inhibitors are a class of biological DMARDs that inhibit pro-inflammatory cytokines other than TNF which are also considered to play a central pathogenic role in the development of rheumatoid synovitis and RA.[1,2] The main non-TNF inhibitors used to treat patients with RA are tocilizumab, abatacept and rituximab.[1,2] Several emerging biological agents are in the pipeline and undergoing clinical trials, eg, ocrelizumab, ofatumumab, epratuzumab and veltuzumab.

Tocilizumab

Tocilizumab is a recombinant humanised monoclonal antibody that binds both soluble and membrane-bound inter-leukin-6 (IL-6) receptors.[3] IL-6 is a pro-inflammatory cytokine found in the synovium of patients with active RA.[2] It acts as a major inducer of the hepatic acute phase proteins, such as C-reactive protein, and serum levels of IL-6 correlate with markers of disease activity in RA. IL-6 promotes osteoclast maturation, which is responsible for bone erosion and radiographic abnormalities in RA.[2,3] The cytokine also plays a role in inducing B-cell differentiation and in T-cell[2] and macrophage activation.[4]

In trials of tocilizumab in patients with RA, clinical improvements were observed as early as four weeks after the initiation of therapy, with improvement becoming most pronounced by week 12.5 Furthermore, data from a one-year open-label trial of 158 patients confirm the superiority of tocilizumab over traditional DMARD therapy in slowing the development of radiographic changes.[4] It is desirable to co-prescribe biological DMARDs with methotrexate, and combination therapy with tocilizumab and methotrexate has been shown to increase the efficacy of the drug.[6]

Indication

Tocilizumab is clinically indicated for the treatment of moderate-to-severe RA. It can be prescribed by rheumatologists (or clinical immunologists with experience managing RA) for the treatment of adult patients with severe active RA who fail to achieve adequate disease remission following either:

- Six months of treatment (including at least three months of continuous treatment) with at least two traditional DMARDs, one of which must be methotrexate unless contraindicated, or
- An unsuccessful trial of therapy with a TNF inhibitor.

Dosing and administration

Tocilizumab is administered as a monthly intravenous infusion. The recommended dose is 8mg/kg administered every four weeks. The maximum recommended dose of tocilizumab is 800mg per infusion.

Side effects

Upper respiratory tract infection was the most commonly documented adverse event associated with tocilizumab in clinical trials.[6] Headache, skin eruptions, stomatitis and fever were less common.[5] Pathology abnormalities encountered during clinical trials included elevated lipid profiles, neutropenia and abnormal levels of liver enzymes.[2] Significant elevations in total cholesterol, triglyceride and HDL levels were also observed, the significance of which is yet to be determined.

Laboratory monitoring of lipid parameters at four- to eight-weekly intervals for the first six months of treatment and at three-monthly intervals thereafter is advisable. Furthermore, the institution

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of cholesterol-lowering agents is sometimes warranted. A dose-dependent, reversible neutropenia can occur at any time during treatment. Treatment interruption may be considered following discussion with the treating specialist if the patient's neutrophil count falls to less than 1 x 10^9U/L.

Transient liver function abnormalities (eg, elevated levels of transaminase and bilirubin) may also occur in a dose-dependent manner, predominantly involving aspartate aminotransferase more than alanine aminotransferase. Treatment interruption may be appropriate in cases where hepatic transaminase levels exceed three to five times the upper limit of normal. In most patients, liver function test abnormalities normalise within eight weeks of the last infusion.[4,6]

Cases of bowel perforation complicating diverticulitis have also been reported in association with tocilizumab therapy. Patients with a history of intestinal ulceration, diverticulitis and concomitant corticosteroid use should be closely monitored for symptoms suggesting potential gastrointestinal toxicity during treatment with tocilizumab.[7]

Abatacept

Abatacept is a soluble fusion protein comprising the human cytotoxic T-lymphocyte antigen 4 (CTLA-4) immunoglobulin and the Fc portion of human IgG1.[2]

RA has traditionally been regarded as a T-cell-mediated disease. In patients with RA, autoantigen-specific T-cells are activated and expand in joints and/or lymph nodes in response to stimulation by antigen-presenting cells (APCs) that convey arthritis-related peptides.[4,8] For T-cell activation to occur in these patients, two equally important processes or signals are required:

- Recognition of a specific antigen by the T-cell – this 'first signal' involves T-cell receptor interaction with the human leukocyte antigen class II molecule on the APC
- A co-stimulatory signal – this 'second signal' involves binding of an APC co-stimulatory ligand to a T-cell receptor, forming a receptor-ligand pair.[9]

Abatacept acts as a selective inhibitor of this co-stimulatory 'second signal' required for T-cell activation. This is achieved by abatacept binding to CD-80 and CD-86 and thus inhibiting T-cell response. Clinical responses to abatacept have been observed as early as day fifteen following treatment initiation. Continued clinical improvements were recorded until trial conclusion at 12 months.[10] This suggests a slightly slower mode of action than the cytokine inhibitors. A statistically significant reduction in radiographical progression compared with placebo after one year of treatment has also been noted.[10]

Indication

Abatacept is indicated in combination with methotrexate for the treatment of moderate-to-severe RA in adult patients who have experienced an insufficient response or intolerance to therapy with traditional DMARDs.

Dosing and administration

Abatacept is dosed according to bodyweight (eg, less than 60kg = 500mg; 60 to 100kg = 750mg; greater than 100kg = 1000mg). Abatacept is administered as a 30 minute infusion and should be given at two and four weeks following the initial infusion, and at four-weekly intervals thereafter.

Side effects

The overall incidence of adverse events in clinical trials was similar in both the abatacept and the placebo-treated groups.[10] The most commonly reported adverse events included headache, nasopharyngitis, dizziness and nausea. Hypersensitivity reactions (hypotension, dyspnoea, urticaria or wheezing) occurred rarely. Serious infections were noted in up to 3.9% of patients receiving combination therapy with abatacept plus methotrexate versus 2.3% of patients treated with placebo plus methotrexate.[10]

It is recommended that GPs therefore remain vigilant for signs of infections that are seen more commonly in patients receiving abatacept (in particular pneumonia [abatacept 0.4% to 0.9% v. placebo 0% to 0.5%]).[10] Other infections to be aware of in patients being treated with abatacept are cellulitis, urinary tract infections and diverticulitis.

Opportunistic infections and malignant diseases are thought to occur at similar frequencies between patients treated with abatacept and placebo.[4,10] Routine laboratory monitoring for patients receiving abatacept follows the same recommendations outlined for TNF inhibitor therapy: three-monthly monitoring of full blood examination, urea and electrolyte levels, liver function tests and inflammatory markers.

Rituximab

Rituximab is a genetically-engineered chimeric human/mouse monoclonal anti-body, directed against the CD20 antigen expressed on the surface of mature and premature B-cells.[2]

B-cells have been shown to play an integral role in the disease pathogenesis of RA. Their pathogenic role is thought to be mediated through either (auto) antibody and/or pro-inflammatory cytokine production, or possibly antigen presentation.[4]

Rituximab is an effective chemotherapeutic agent in the treatment of CD20 positive B-cell non-Hodgkin's lymphoma and was initially approved for this indication.[11] Recognition of rituximab's therapeutic potential in RA is a more recent development.[12] Treatment with rituximab causes transient depletion of CD20-positive B-cells. This occurs without affecting stem cells or plasma cells, thereby allowing new B-cells to develop after six months.[11,13]

In clinical trials for RA, B-cell depletion occurred rapidly, as assessed by CD19 positive cell counts. Response to rituximab was apparent within eight weeks of treatment, with changes in radiographical endpoints showing a trend towards slower progression of joint damage in rituximab-treated patients.[4,14]

Indication

Rituximab is considered a second-line biological DMARD and is indicated in combination with methotrexate for the treatment of adult patients with severe RA. Patients should demonstrate an inadequate treatment response to at least one TNF inhibitor before receiving rituximab therapy.

Dosing and administration

Rituximab is administered intravenously

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TABLE
Non-TNF inhibitors[1,2]

Non-TNF inhibitor biological DMARDs	Route of administration	Mechanism of action
Tocilizumab	Monthly IV infusion of 8mg/kg (to maximum of 800mg)	Monoclonal antibody to IL-6 receptor
Abatacept	Monthly IV infusion dosed according to bodyweight (<60kg = 500mg; 60 to100 kg = 750mg; >100kg: 1000mg), following an initial loading dose given at zero, two and four weeks	CTLA-4–1gG1 fusion protein, an inhibitor of T-cell co-stimulation
Rituximab	Two 1000mg IV infusions given two weeks apart. Repeat dosing is not usually given for at least six months following the first infusion	Chimeric monoclonal antibody binding to CD-20 on premature B-cells

ABBREVIATIONS: TNF = tumour necrosis factor; CTLA-4 = cytotoxic T-lymphocyte antigen 4; CD-20 = cluster of differentiation 20; DMARD = disease-modifying antirheumatic drug; IgG1 = immunoglobulin G subclass 1; IL-1 = interleukin 1; IL-6 = interleukin 6; IV = intravenous; SC = subcutaneous

as two doses of 1000mg, given two weeks apart. Rituximab can be administered concomitantly with the dose of methotrexate tolerated by the patient. The timing of retreatment is largely determined by disease activity, but rituximab therapy is generally not repeated until 24 weeks after the first infusion.[4]

Side effects

Acute infusion reactions (eg, pruritus, rash, urticaria/angioedema, fever, chills, rigors, bronchospasm, with or without alterations in blood pressure) are the most commonly reported adverse events associated with the use of rituximab for RA. Reactions occur most often during (or within 24 hours of) the first infusion, and tend to abate with subsequent doses. The rate of serious infections necessitating intravenous antibiotics per 100 patient-years was 3.7 in the placebo group versus 5.2 for rituximab-treated patients.[14] The most common infections reported in both groups were upper respiratory tract infections, nasopharyngitis, urinary tract infections, bronchitis and sinusitis.

GPs should therefore remain vigilant for signs of infections affecting these systems and implement appropriate antimicrobial therapy as needed. There was no suggestion of increased incidence of malignant diseases or opportunistic infections associated with rituximab in clinical trials.[4] Routine laboratory monitoring for patients receiving rituximab follows the same recommendations outlined for TNF inhibitor therapy and as stated previously for abatacept.

Development of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain, has been associated with the use of rituximab. Patients who develop new or worsening neurological symptoms or signs suggestive of PML require a complete neurological assessment, including a physical examination, an MRI scan and CSF testing for John Cunningham viral DNA. Rituximab must be permanently discontinued if a diagnosis of PML is confirmed.[12]

Which biological DMARD is most effective?

As more biological DMARDs become available, an important question arises in clinical practice: 'Which biological DMARD is the most effective agent for treating RA in patients who fail to respond to traditional DMARD therapy?'

To date, no head-to-head comparisons have been performed to answer this question. The final decision on which biological DMARD to use is ultimately influenced by the available evidence and by factors including, but not limited to, an individual patient's comorbidities and preference.

Emerging therapies

Although a cure for RA remains elusive, the search for new medications and better treatment strategies remains the focus of ongoing research. A large and promising group of emerging therapies involves targeting molecules intrinsic to the intracellular signal transduction pathways involved in the pathogenesis of RA. Therapeutic targets identified within this class of biological agents include the Janus-kinase/signal transducer and activator of transcription (JAK/STAT) pathways, spleen tyrosine kinase (Syk) and the mitogen-activated protein kinases (MAPKs).[17]

Therapeutic targets

JAK/STAT

JAK binds the cytoplasmic region of transmembrane-cytokine receptors, resulting in STAT activation, which acts as a transcription factor. There are four JAK subtypes, of which JAK3 plays an essential role in signal transduction for IL-2, IL-4, IL-9, IL-15 and IL-21. These interleukin pathways are integral to lymphocyte activation, function and proliferation.

In phase II clinical trials, a new oral JAK3 inhibitor tofacitinib has been reported to bring clinical improvement as early as 12 weeks in measurements of pain, disability and quality of life. Phase III studies have been reported in poster format showing similar efficacy.[17,18]

Syk

Syk is an important mediator of immunoreceptor signalling in macrophages, neutrophils, mast cells, synovial fibroblasts and B-cells. The net downstream effect of Syk activation includes increased IL-6 and matrix metalloproteinase production. A recently published phase II clinical trial confirmed the positive impact of Syk inhibition on reducing disease activity, and supported the Syk pathway as a potential new drug target for the treatment of RA.[19]

MAPKs

MAPKs are intracellular enzymes that transmit signals to the nucleus, resulting in gene transcription. They have been found in the synovial lining and endothelium of vessels within RA synovium. MAPKs have been implicated in regulating TNF, IL-1 and IL-6 signalling, and animal studies demonstrated their efficacy in reducing joint swelling and damage.[4,6]

New generation monoclonal antibodies

New generation monoclonal antibodies are also on the horizon for RA treatment. Following the success of rituximab, four new humanised B-cell-depleting therapies are under current evaluation: ocrelizumab, ofatumumab, epratuzumab, and veltuzumab. Research is also under way on developing monoclonal antibodies against novel targets, such as IL-17 (secukinumab) and the haemopoietic regulators, granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor (mavrilimumab).[17]

Conclusion

Methotrexate remains the drug of choice for the treatment of patients with active RA. There is evidence it is equally efficacious as the biological agents in the treatment of early RA. In patients whose disease is inadequately controlled either with methotrexate treatment or with a combination of other non-biological DMARDs, there is an array of highly effective agents that are now available to treat the disease. The availability of these emerging biological agents has radically changed the approach towards RA management.

The prescription of these new therapies remains in the domain of the specialist rheumatologist (or immunologist with experience in managing RA). However, GPs play a vital role in providing early patient referral for specialist evaluation and partnering with specialists in monitoring patients for the development of treatment- and disease-related complications. The expectation of treatment is now no longer simply to palliate patient symptoms, but to move patients with early RA into long-term remission.

References are available on request.

Non-Specific Low Back Pain

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Role of surgery

There is a limited role for surgery in treating patients with low back pain. Decompression surgery may be effective for improving leg pain in patients with spinal stenosis but the value of discectomy, disc replacement and fusion for non-specific low back pain is unclear at best. In all cases, a trial of nonsurgical management before surgical opinion is appropriate. For patients with radiculopathy, although surgery can provide short-term pain relief, long-term outcomes may be comparable to conservative management.

Prevention of low back pain

Effective prevention of low back pain is not well understood. This applies to both primary and secondary prevention. There is some evidence to support the influence of increasing physical exercise and improving education levels, specifically the understanding of low back pain as a biopsychosocial condition.[39] Education should also promote a shift in beliefs regarding the consequences of low back pain, particularly work absence, fear of physical activity and implications for continuing daily activities.[40]

Conclusion

Low back pain is a prevalent and costly health condition and is the most common musculoskeletal reason for seeking primary care. Serious conditions relating to low back pain present extremely rarely in general practice and investigations for these are recommended only if red flags are present. The prognosis for patients with short-term symptoms of non-specific low back pain is good, and initial management involves advice to maintain physical activity, reassurance and the provision of simple analgesia. If symptoms persist, stronger medication and physical therapies can be recommended. Multi-disciplinary rehabilitation clinics provide an option for patients with severe, disabling symptoms of long duration. Clinicians should avoid providing pathoanatomical labels, and there is no place for routine imaging or pathology tests in patients with non-specific low back pain.

References are available on request.