ARTICLE

# Infliximab in Rheumatic Diseases

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Infliximab is a chimeric IgG1 monoclonal antibody against tumour necrosis factor-a (TNF-a). Infliximab is indicated, for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC) and skin psoriasis. The first aim of this article is to revisit the indications for the use of infliximab in RA, AS and PsA. The second aim is to get an update on the newest insights on the safety and efficacy of the drug.

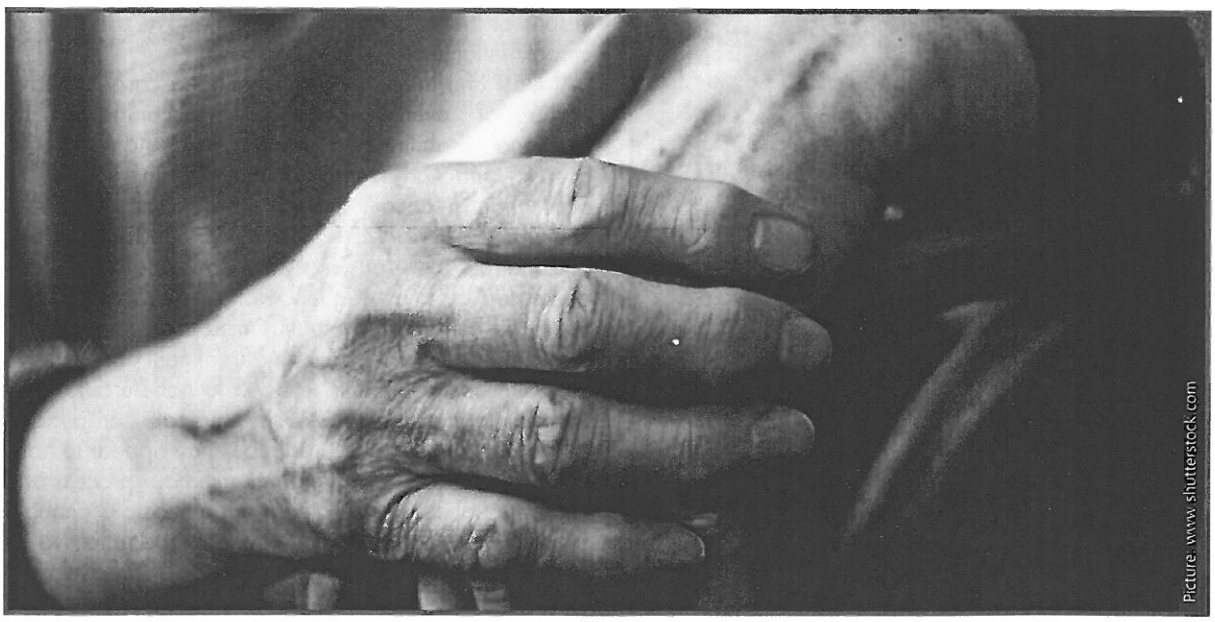
## Rheumatoid arthritis

RA is a chronic inflammatory disorder that mainly targets the synovial membrane, cartilage and bone, and affects 1% of the population. A number of cytokines, which are expressed and functionally active in the synovial tissues, are involved in the immune processes that are associated with the pathogenesis of RA. Amongst the cytokines, which regulate a broad range of inflammatory processes, the tumour necrosis factor alpha (TNF-) has become a major target in the treatment of patients with RA.

Infliximab in combination with methotrexate (MTX) is indicated for the reduction of signs and symptoms, as well as the improvement of physical function in:

1. Adult patients with active disease when the response to disease modifying anti-rheumatic drugs (DMARDs), including MTX, has been inadequate. Two important studies have been done in this regard: The antitumor necrosis factor trial in RA with concomitant therapy trial, a phase III randomised, double-blind, placebo-controlled, multicenter trial that evaluated 428 patients with active RA despite continuous MTX treatment and the safety trial for RA with REMICADE® Therapy trial, a phase IIIb randomised, multicenter, placebo-controlled study that assessed 1084 active RA patients with various co-morbidities, who received infliximab in combination with MTX. Adult patients with severe, active and progressive disease not previously treated with MTX or other DMARDs. The active-controlled study of patients receiving infliximab for the treatment of RA of early onset trial, a phase III randomised, double-blind, placebo-controlled study focused on 1049 active RA patients with a disease duration of ≤3 years. In these patient populations, a reduction in the rate of the progression of joint damage, as measured by x-ray, has been demonstrated.

Insights into the safety and efficacy of infliximab, as well as treatment strategies for the management of RA patients, have been provided by studies such as the Behandel-Strategieën (BeSt) treatment strategies study,



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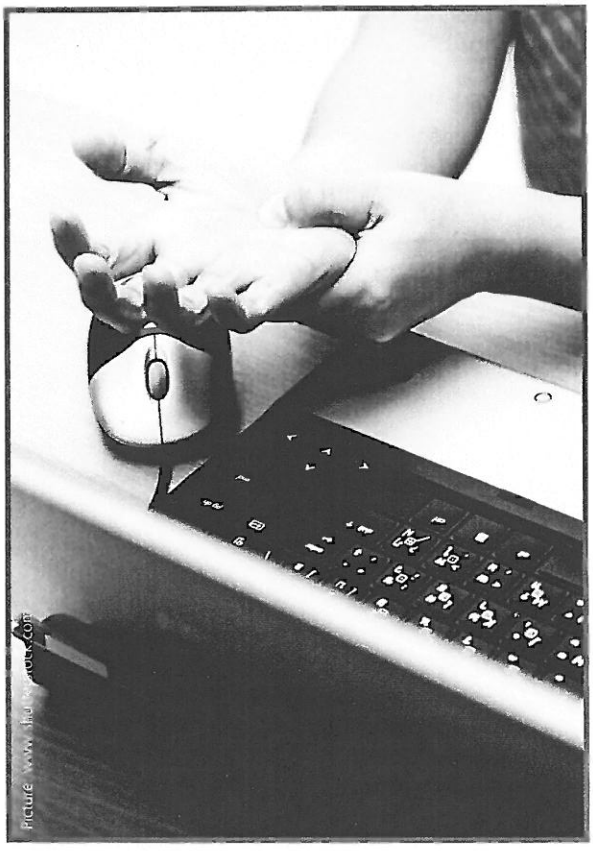
a prospective long-term study in MTX-naïve early RA patients to evaluate the use of four different treatment strategies to achieve a target outcome of low disease activity (LDA). The proportion of patients on each treatment step at five-years varied among groups. The initial monotherapy groups (one and two) needed more treatment adjustments before achieving a disease activity score (DAS) of 2.4 or less than the initial combination therapies (groups three and four).

After five years, 25%, 21%, 45% and 65% of patients in groups one to four respectively were still on the initial treatment step. Half of the patients in group four had permanently discontinued the initial treatment with infliximab because of a continuous low disease activity, and 46% of patients in group three had successfully tapered and stopped prednisone. In groups one to three 41%, 12% and 21% respectively had started delayed infliximab because of insufficient response to previous drugs, and 21%, 5% and 11% respectively were still treated with infliximab at five years, compared with 19% in group four.

Another study was the Swedish pharmacotherapy study, a trial comparing the safety and efficacy of adding infliximab or a combination of DMARDs in early RA patients who showed an inadequate response to MTX. The study confirmed the findings of BeSt, showing that in patients with early RA in whom MTX treatment failed, addition of a TNF antagonist to MTX monotherapy is clinically superior to the addition of conventional DMARDs.



A total of 487 patients were initially enrolled. Of 258 patients who had not achieved low disease activity with MTX, 130 were allocated to add sulfasalazine and hydroxychloroquine (DMARD combination) and 128 were assigned to receive infliximab in addition to MTX. A total of 32 of 130 patients (25%) allocated to the DMARD combination regimen achieved the primary outcome compared with 39% (50/128) of those assigned to MTX plus infliximab (risk ratio 1·59 [95% CI 1·10–2·30], p=0·0160). Adverse events were balanced fairly well between the two groups and no deaths occurred in either group.

More data on the benefit-risk of infliximab among RA patients have arisen from registry data.

## Ankylosing spondylitis

AS is a chronic, progressive, inflammatory disease that generally begins early, when the patient is 20-30 years old, and remains underdiagnosed. Prevalence estimates vary across studies and countries, from 0.6 to 1.9%. Women are not as commonly affected as men, but the overall disease impact may be similar. Although the exact etiology of AS is unknown, a genetic component, mainly specific HLA-B27 subtypes and bacteria seem to be crucial for development of disease.

Inflammation of sacroiliac joints, the spine, and entheses leads to new bone formation, syndesmophytes, and ankylosis of joints resulting in restricted mobility. Patients with AS may also have associated peripheral arthritis, enthesitis and osteoporosis accompanied with an increased risk for fractures. Acute anterior uveitis is the most common extra-articular manifestation of AS, occurring in 25%-30% of patients. Additionally, 25% to 50% of patients with AS may have microscopic inflammatory lesions of the colon, and about 7% have a history of chronic inflammatory bowel disease.

At least one third of patients with AS carry a heavy burden of severe disease often accompanied by functional disability and unemployment. Admissions to hospital and early retirement have been reported to occur more frequently than in the general population. The disease itself is associated with substantial direct and indirect costs for society. Patients' quality of life is decreased as a consequence of the functional limitations and handicap, the pain linked to disease activity and the reduced work capacity. Treatment options have been limited for patients with AS to non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy and DMARDs. NSAIDs relieve pain but they appear to have little effect on the underlying inflammatory process and for some patients, NSAIDs are not efficacious enough. DMARDs have not been proven to be effective in patients with spinal manifestations of AS. Sulfasalazine may provide benefit for peripheral articular manifesta-

tions of AS but it has not been shown to be effective in treating axial disease.

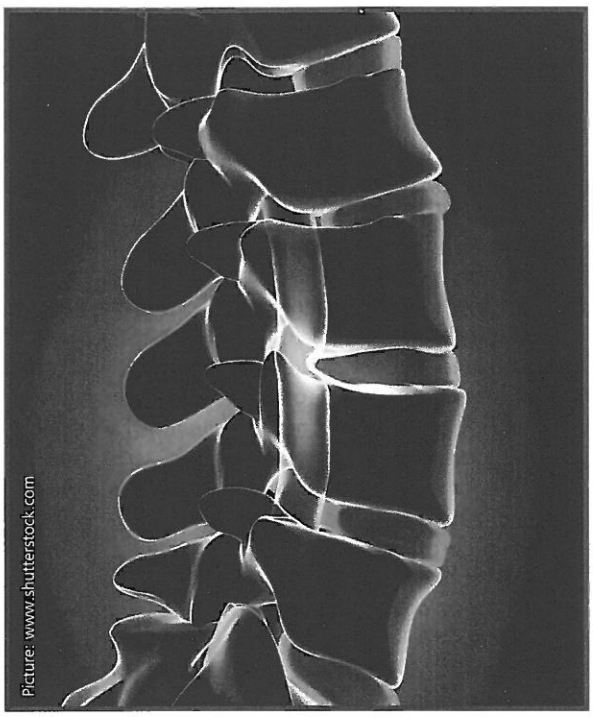
Abundant TNF- messenger RNA has been detected in sacroiliac joints of patients with AS. It is widely accepted that the overproduction of the cytokine TNF- stimulates an inappropriate inflammatory response. Anti-TNF-α therapy, such as infliximab, has the potential to influence the underlying inflammatory process by blocking the pro-inflammatory cytokine TNF-α and is likely to change the therapeutic approach to AS patients.

Recent efforts from the Assessment of SpondyloArthritis International Society (ASAS) and European League Against Rheumatism (EULAR) have provided relevant insight on both spondyloarthritis classification criteria and recommendations for the management of AS. Infliximab is indicated for treatment of severe, active AS, in adult patients who have responded inadequately to conventional therapy.

The efficacy and safety of infliximab was initially evaluated in a placebo-controlled, double-blind, randomised, multicenter study in 69 patients with active AS. Infliximab resulted in significant improvement in disease activity as measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 through week 12 compared to those patients who received placebo. Improvement was observed as early as week two. Evaluation of spinal inflammation demonstrated a significant regression in acute and chronic inflammation with infliximab compared to only a slight improvement and even deterioration for patients treated with placebo through 12 weeks. Patients receiving infliximab were more likely to have improvement of the peripheral arthritis and enthesitis and to reduce or discontinue NSAIDs than those patients who received placebo. The significant improvement in disease activity (BASDAI), functional assessment (BASFI), mobility of the spine and hips (BASMI), quality of life (SF36) and laboratory parameters (ESR, CRP) was sustained over the open-label period of 54, 102 and 158 weeks. Safety results were consistent with those from other clinical pivotal infliximab trials.

After three years of maintenance treatment with infliximab, all patients discontinued treatment and were eligible to enter another two-year extension phase. Infliximab was safely re-administered and showed persistent clinical efficacy and safety over eight years. Based on the results of this study, infliximab was approved for the treatment of severe active AS, in adult patients who have responded inadequately to conventional therapy.

The efficacy and safety of infliximab was further evaluated in a larger patient population: The Ankylosing Spondylitis Study For the Evaluation of Recombinant Infliximab was a randomised, double-blind, placebo-controlled, multicenter study in 279 patients with active AS. Significantly more infliximab-treated patients (61%)




achieved an Assessment of Assessment of Spondylo Arthritis (ASAS) 20 response, compared to patients receiving placebo (19%) at week 24($p<0.001$). Infliximab reduced BASDAI, and improved BASFI and BASMI significantly better than placebo. Improved spinal mobility persisted through two years. Patients receiving infliximab had a highly significant decrease in spinal inflammation assessed by MRI from baseline to week 24. The mean change in MRI activity scores was -0.6 with infliximab versus -5.0 with placebo ($p<0.001$), an effect that persisted for at least two years in patients who continued treatment. The improvement with infliximab in ASAS 20 was consistent across all pre-specified subgroups including gender, disease duration, age, baseline disease activity and physical function, HLA-B27 genotype and CRP status. Safety results were consistent with those from other pivotal infliximab clinical trials.

Infliximab is effective for reducing clinical and imaging evidence of disease activity in patients with MRI-determined early axial spondyloarthritis. Further to the clinical trial data, there are reports on the long-term use of infliximab in patients with AS. Treatment with infliximab also significantly increased the bone mineral density in patients with refractory spondyloarthropathy.

Further information on the benefit-risk profile of infliximab among AS patients has arisen from registry data.

## Psoriatic Arthritis

PsA is an immune mediated inflammatory disorder that affects 10%-30% of patients with psoriasis. Also characterised as a spondyloarthropathy, disease mani-

festations can involve axial and peripheral joints, nails, and entheses, and are usually accompanied by psoriatic skin lesions. The course of PsA is variable, and up to 95% of patients may have swelling in joints outside the spine. TNF-α has been associated with the pathogenesis of PsA. Increased concentrations of TNF-α have been reported in joint fluid/tissue, and in psoriatic skin lesions. TNF-α has also been shown to play an important role in the induction and perpetuation of the inflammatory process in PsA joint tissue and psoriatic skin lesions. Therefore, therapy directed at reducing TNF-α may also be beneficial in PsA.

Several independent studies provided the first results on the benefits of the use of infliximab in the management of PsA patients. The management of PsA patients has changed dramatically over recent years and the complexity of the disease as well as more recent insights have contributed to the development of the recently published European League Against Rheumatism recommendations.

Infliximab is indicated for the treatment of active and progressive PsA in adult patients when the response to previous DMARD therapy has been inadequate. Infliximab should preferably be administered in combination with MTX but can be used alone in patients who show intolerance to MTX or for whom MTX is contraindicated. Infliximab has been shown to improve physical function in patients with PsA, and to reduce the rate of progression of peripheral joint damage as measured by x-ray in patients with polyarticular symmetrical subtypes of the disease.

The safety and efficacy of infliximab in PsA was first assessed in the induction and maintenance psoriatic arthritis clinical trial, a double blind, placebo-controlled, multicenter study evaluating 104 patients with active polyarticular PsA.

Treatment with infliximab resulted in an improvement in signs and symptoms, with 65% of infliximab treated patients achieving an American College of Rheumatology (ACR) 20 response at week 16, compared to 10% of placebo-treated patients ($p<0.001$). Improvement was observed as early as week two, and was maintained through week 98.

Decrease in parameters of peripheral activity characteristic of PsA, such as number of swollen and painful joints, and the presence of dactylitis or enthesopathy, was seen in the infliximab-treated patients. Infliximab-treated patients also demonstrated improvement in physical function and skin disease, and showed inhibition of radiographic damage at weeks 50 and 98.

The safety and efficacy of infliximab in PsA was further investigated in the Infliximab Multinational Psoriatic Arthritis Controlled Trial (Impact) II, a phase III, randomised, double-blind, placebo-controlled, multicenter trial of 200 PsA patients. Through 54 weeks, Impact II study investigators concluded that treatment with infliximab significantly reduced clinical signs and symptoms of PsA, including dactylitis and enthesopathy, and improved psoriatic skin disease, physical function, and quality of life in patients with PsA. Infliximab significantly inhibits radiographic progression in PsA patients, as early as 24 weeks after starting treatment, and the beneficial effect continues through week 54. The safety profile of infliximab through week 54 was consistent with that see through week 24. Two malignancies were reported: a basal cell skin cancer in a placebo patient and a stage I Hodgkin's lymphoma in an infliximab treated patient.

## Dosage for use of infliximab

Infliximab is given as an intravenous infusion over a two-hour period. Infliximab treatment is to be administered under the supervision of a specialised physician experienced in the diagnosis and treatment of these diseases.

## Conclusion

Infliximab is the longest available biologic drug. It has been proven to be effective and in the clinic we witness the difference it has made in the quality of life of numerous patients. Although some patients have not benefitted and some unfortunately did suffer from side-effects, the benefit-risk ratio still favours the drug, e.g. used for the right indication most patients will improve.

## Limitations of the article

In this article no comparison with regards to long-term efficacy and safety was made to other biologic drugs.

***References available on request.***

| Diagnosis | Dose | Interval |
|---|---|---|
| Rheumatoid arthritis (+ MTX) | 3mg/kg | Induction: weeks zero, two and six<br>Maintenance: every eight weeks thereafter |
| Ankylosing spondylitis | 5mg/kg | Induction: weeks zero, two and six<br>Maintenance: every six to eight weeks thereafter |
| Psoriatic arthritis | 5mg/kg | Induction: weeks zero, two and six<br>Maintenance: every eight weeks thereafter |
| *Please refer to package insert for preparation and administration guidelines | | |