
Infliximab for psoriasis and psoriatic arthritis

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ABSTRACT

Tumor Necrosis Factor alpha (TNF) as proinflammatory cytokine plays in the pathogenesis of many diseases an important role. In psoriasis and in psoriatic arthritis TNF is up-regulated in the skin lesion and in the synovitis. Recent trials showed that the blockade of TNF with the chimeric antibody infliximab is able to improve both, the skin lesions and the synovitis of the joints. In psoriasis in 82 % of patients treated with infliximab achieved an over 75% response in the PASI index. In Psoriatic arthritis the skin improvement was correlating with the reduction of synovitis and in a small MRI controlled study all patients achieved an ACR 20 response within 10 weeks. Patients with psoriatic arthritis, who have been included in spondylarthropathy trials showed similar improvement rates. In all trials unexpected safety problems have not been reported, but the trials have been small in population and short in duration. Infliximab was used between 5 and 10 mg/kg at week 0, 2, 6 and every 8 week. In some trials the retreatment periods varied. In contrast to the treatment of rheumatoid arthritis with infliximab methotrexate was not always used as comedication. In some cases infliximab has been used in combination with other DMARDs but no trial did evaluate the combination treatment vs. the monotherapy.

Introduction

TNF blockade with infliximab in rheumatoid arthritis, has been the first biologic therapy, which proved to be effective in rheumatoid arthritis. The unexpected grade of success the therapy showed, lead to further investigation of the treatment principle in diseases with similar pathogenesis like psoriasis and psoriatic arthritis. In psoriasis epidermal hyperproliferation, inflammatory infiltration are driven by activated T-cells or antigen-presenting cells, from which proinflammatory cytokines are released. TNF plays a major role within these cytokines. In psoriatic arthritis

TNF is elevated in the skin lesion and in the synovial fluid.

Psoriasis

Chaudhari *et al.* performed the first double-blind trial comparing infliximab with placebo in 33 patients with moderate to severe plaque psoriasis (1). The patients were randomly assigned into three treatment arms with placebo (n=11), infliximab 5 mg/kg (n=11), or infliximab 10 mg/kg (n=11). The infusions have been given at weeks 0, 2, and 6. Patients were assessed at week 10 for the primary endpoint [score on the physician's global assessment (PGA)]. Analysis was by intention to treat. Of the 33 patients enrolled, three dropped out.

In the infliximab 5 mg/kg group, 9 of 11 (82%) patients were responders (good, excellent, or clear rating on PGA), compared with 2 of 11 (18%) in the placebo group (difference 64% (95% CI 20-89), $p=0.0089$). In the infliximab 10 mg/kg group 10 of 11 (91%) patients were responders (difference from placebo 73% (30-94), $p=0.0019$). The secondary endpoint in this trial was the change in the Psoriasis Area and Severity Index (PASI). The improvement by at least 75% is considered clinically meaningful and beside the mean improvement in PASI the percent of patients who reached the 75% improvement is important. In the 5 mg/kg group 9 (82%) and in the 10mg/kg group 8 (73%) patients reached a 75% improvement in their PASI compared to 2 (18%) in the placebo group (Fig. 1). The mean PASI score changed from 22,1 in the 5 mg/kg group, 26,6 in the 10 mg/kg and 20,3 in the placebo group to 3,8; 5,9 and 17,5 respectively ($p < 0.0003$). The difference between placebo and both treatment groups was significant from week 2 ($p < 0.0003$) of treatment and the median time to response was 4 weeks for patients in both infliximab groups. There were no serious adverse events, and infliximab was well tolerated.

In this controlled trial, patients receiv-

ing the anti-TNF- α agent infliximab as monotherapy experienced a high degree of clinical benefit and rapid time to response in the treatment of moderate to severe plaque psoriasis compared with patients who received placebo. These findings suggest that TNF- α has a pivotal role in the pathogenesis of psoriasis and that the treatment with infliximab as monotherapy is effective. These patients have been followed up to 26 weeks without further treatment. It showed that 55% of the patients continued to have a PASI 50% response and 48% of the patients still showed a PASI 75% response at week 26 (Gottlieb A. et al. presented at the AAD meeting 2002). Gottlieb also showed histology probes of the involved skin, that the treatment with infliximab leads to decrease of inflammation in the skin and to normalization of the keratinocyte differentiation.

Beside this one double blind trial some small cohorts have been published. Ogilvie *et al.* reported about the skin improvement in the open label treatment of 6 patients with psoriatic arthritis. All 6 patients received infliximab at week 0, 2 and 6 5 mg/kg. Five patients had concomitant methotrexate and one sulfasalazine. The median PASI improvement was 71% and three patients reached an improvement over 75% (2). Schopf *et al.* treated 8 patients with severe psoriasis in an open-label clinical trial. Patients received infliximab, 5 mg/kg, intravenously at weeks 0, 2, and 6. The Psoriasis Area and Severity Index (PASI) was used as endpoint at week 10. In this trial beside the PASI pruritus was assessed on a scale of 0 to 3 and histologic sections were prepared from biopsy specimens of uninvolved skin and of psoriatic lesions at weeks 0, 1, and 10 to measure epidermal thickness with the use of a microscopic micrometer grid. The PASI reduced from 21.8 ± 4.2 (mean $\pm$ SE) at week 0 to 3.4 ± 2.0 at week 10, by $89.3\% \pm 4.3$. Pruritus decreased from 2.5 ± 0.26 at week 0 to 0.43 ± 0.2 at week 10. In the biopsies the epidermal thickness (acanthosis) tended to normalize from 0.41 ± 0.06 mm at week 0 to 0.14 ± 0.02 mm at week 10. No adverse effects other

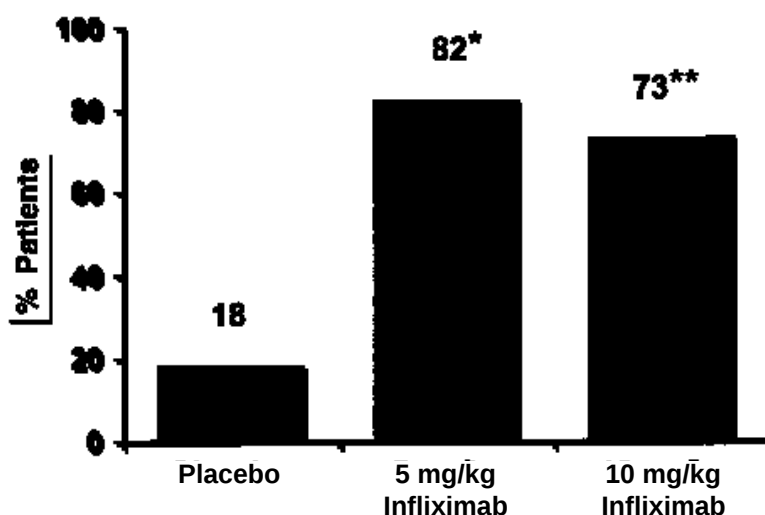


Fig. 1. Percent of patients with *75% improvement in PASI at week 10 in a double blind psoriasis trial (*0.009, **0.030).

than fatigue during infusion on some occasions were reported (3). Quinn *et al.* reported two patients with recalcitrant psoriasis that have been unresponsive to multiple skin-directed and systemic therapies. Patients were treated with a single infusion of infliximab. The treatments resulted in rapid and complete clearing of psoriatic erythroderma in one patient and clearing of widespread psoriatic plaques in the other (4). Kirby *et al.* reported about the successful combination of Infliximab with Methotrexat in the treatment of psoriasis (5). At the moment a phase III trial is starting to evaluate the efficacy and safety of infliximab in psoriasis in further detail.

Psoriatic arthritis

The efficacy of infliximab in psoriatic arthritis (PsA) have been investigated in double blind trials together with other spondylarthropathies and in an open label MRI controlled trial with PsA. A 100 patient double-blind placebo controlled trial in PsA is ongoing. In the MRI controlled trial 10 patients have been treated with infliximab 5 mg/kg at week 0, 2 and 6 (6). The primary endpoint was week 10. The co-medication was kept stable with steroids ≤ 10 mg/kg. Seven patients were taking methotrexate, 1 patient was using sulfasalazine, and 2 patients have been without any DMARD. The ACR

criteria of improvement, the PASI and a MRI of the most involved peripheral joint area has been performed at baseline and week 10. As outcome criteria has been used the Clegg and the ACR criteria (7,8). After 10 weeks all patients reached the Clegg criteria, the ACR20 and 50 % improvement and 8 patients reached the ACR70%. The MRI showed a mean reduction of the gadolinium uptake by $82.5\% \pm 10.3\%$ ($p = 0.0071$). The PASI was reduced by $72.3\% \pm 16.7\%$ ($p = 0.0321$) and an improvement $\geq 75\%$ PASI was reached by 50% of the patients with skin involvement. All patients have been followed for 54 weeks with individual treatment regimens. One patient continued with 5 mg/kg every 8 weeks, 4 patients reduced therapy to 3 mg/kg every 8 weeks and 5 patients discontinued therapy at week 10 and month 5, 7 and 8 respectively. From these 5 patients 4 discontinued due to remission and 1 because of pregnancy and infusion reaction. At week 54 all 10 patients still reached the Clegg criteria and the ACR20 and ACR50% improvement. The ACR70% have been kept by 6 patients (Fig 2). Beside the one infusion reaction, which was treated with antihistamines no significant adverse event has been observed. The same patient became pregnant and discontinued due to both events. The patient gave birth to a healthy child at term. In

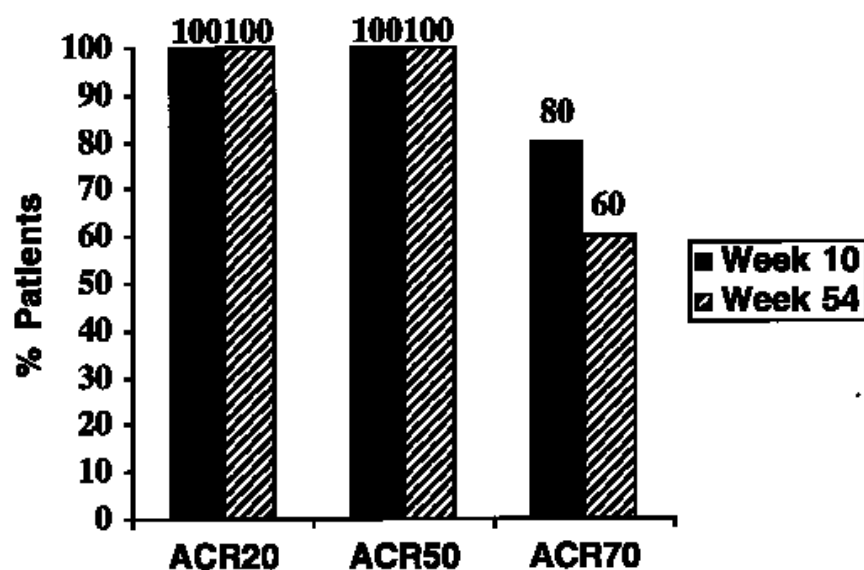


Fig. 2. ACR response at weeks 10 and 54 in an open label PsA trial.

conclusion this was the first study which proved by MRI and skin evaluation that the TNF blockage with infliximab reduces both the inflammation of the skin and the synovitis of the joint in the same way.

Van den Bosch *et al.* investigated 40 patients with active spondylarthropathy (SpA) in a double blind trial (9). The patients were randomised to receive either 5 mg/kg infliximab or placebo at week 0, 2, and 6. The follow up was up to week 12. The primary endpoint was the improvements in the patient and physician global assessments of disease activity on a 100-mm visual analog scale (VAS). In the study were included patients with ankylosing spondylitis (AS), PsA and undifferentiated SpA (uSpA). Because of the clinically different picture of the diseases included in the SpA there are no validated disease activity criteria. The study used as inclusion criteria one swollen joint or one concurrent episode of active tendinitis or dactylitis and/or inflammatory pain of the spin. Concurrent DMARD treatment had to be discontinued 4 weeks before baseline. Included were 9 patients with AS 10 patients with AS and peripheral joint involvement, 18 patients with PsA and 3 patients with uSpA.

Both primary endpoints (patient and physician global), patient assessment of pain and CRP became significant vs.

placebo from week 1 onward until week 12 ($p \leq 0.001$ at week 12 for all parameters). The assessment of night pain improved significantly from week 2 onwards. 30 patients have been assessed for peripheral joint involvement (≥ 1 swollen joint). The morning stiffness, the peripheral joint pain on a VAS, and the tender joint count reached significant improvement vs placebo the swollen joint count did not. In patients with axial involvement (21 patients) the BASFI and the BASDAI reached at week 12 significant improvement vs. placebo ($p = 0.041$ and $p = 0.002$). The PASI was evaluated but because of significant difference at baseline between treatment groups (mean PASI of 0.235 in the infliximab vs. 8.9 in the placebo group) no conclusion was drawn and the endpoint data has not been reported. One patient developed 3 weeks after the third infusion high-peaking fever and was finally diagnosed with extrapulmonary tuberculosis (spleen, liver and mediastinal lymphnodes). Another patient had a suspected joint infection after synovial biopsy at week 1, and recovered completely after initiation of antibiotic treatment within 48 hours. All other adverse events were not significantly different between the treatment groups.

The study showed in a double blind trial that infliximab is able to reduce inflammation in the different diseases

of the SpA group beside reactive arthritis. Patients with this diagnosis have not been included in the trial. Because of the heterogeneity of the clinical pictures and the different inclusion criteria compared to other trials in PsA the results are not compare-able with other trials in PsA. Outcome measurements like the Clegg or ACR20 criteria can not been used because of the missing joint counts at baseline. The same is true for the skin involvement of the patients with PsA. The imbalance at baseline made an evaluation of the skin response to infliximab impossible. In an earlier open label trial with 21 patients with SpA the same results have been seen (10). The global assessments showed significant improvements but the joint counts and the PASI have been hard to evaluate because of low values at baseline.

Conclusion

TNF is an important mediator of inflammation in the skin and in the synovitis of patients with psoriasis and PsA. The blockage of the biologic active TNF with the chimeric monoclonal antibody infliximab showed significant improvement in both the skin and joint lesions. Not at least this dramatic clinical response in both areas is an argument that TNF plays a pivotal role in the pathogenesis in psoriasis and in PsA. In contrast to the anti-T-cell treatment used in psoriasis, the anti-cytokine treatment is effective in both disease entities. It is not clear yet if the mechanism of action is equal in the joint and in the skin. Infliximab showed a reduction of the PASI by 75% in 82% of the psoriasis patients and in 50% of the patients with PsA. Other biologicals which are currently tested in psoriasis are antibodies against CD11a, CD80, a subunit of the IL-2 receptor and the CTLA4Ig; they all reach PASI 75% improvements between 10 and 50% of the cases (11). Etanercept has been recently approved for the treatment of PsA in the USA. Whereas the reduction of inflammation in the joint is comparable between infliximab and etanercept the reduction of PASI $\geq 75\%$ was only reached in 26% of patients treated with etanercept vs. 70 to 82% of the

patients treated with infliximab in psoriasis. If the difference is due to the different patient population or if it is due to differences in the pharmacokinetic of both drugs is not known. Infliximab is able to trigger complement mediated cell-lysis of TNF-expressing cells *in vitro* (12). It is unclear if the same is true for etanercept (13). In addition another work showed differences in the stability of TNF-binding between etanercept and infliximab (14). If the higher stability of the TNF/infliximab complex vs the TNF/etanercept complex and the ability of cell lysis plays a role in the difference between the two drugs can not be answered yet. In difference to RA all studies used 5 mg/kg as fixed dose. This is mainly because no trial had the resources to run proper dose finding arms. Therefore 5 mg/kg have been chosen without scientific proof. Another difference has been that all trials had no methotrexate background therapy. In psoriasis and SpA no DMARD have been allowed and in the small PsA trial different DMARD as stable co-medication have been used. So far there is no data which suggest that patients in these trials without background DMARD therapy develop less efficacy, higher infusion reactions or antibodies against infliximab than patients in the RA trials which have to be on methotrexate therapy. All trials

have been small in size and it needs further double blind trials to proof the efficacy and safety of infliximab in psoriasis and PsA. At the moment one investigator driven trial with 100 patients investigates double blind the efficacy and safety of infliximab in PsA and a phase III trial in psoriasis will start shortly.

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