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Are TNF-α inhibitors Infliximab and Certolizumab pegol effective in treating adults with Psoriatic Arthritis (PsA) or PsA patients who have previously failed disease-modifying anti-rheumatic drug (DMARD) therapy?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether "TNF-α inhibitors Infliximab and Certolizumab pegol are effective in treating adults with Psoriatic Arthritis (PsA) or PsA patients who have previously failed disease-modifying anti-rheumatic drug (DMARD) therapy

Study Design: Review of three randomized, double-blind, placebo controlled clinical trials published after 2006.

Data sources: Three articles were found on PubMed and chosen based upon patient oriented outcomes relevant to the patient population. The population study was adults with psoriatic arthritis (PsA) and patients with PsA who failed prior DMARD therapy. Infliximab and certolizumab pegol were analyzed for treatment efficacy.

Outcomes: There were three outcomes measured, looking at different angles to assess the efficacy of infliximab and/or certolizumab pegol. ACR 20 response was the endpoint chosen in one study, household productivity was chosen for another study, and PASI 75 response was the primary outcome in the last study.

Results: Atteno et al[2] showed a statistically significant ACR 20 response in patients treated with infliximab. Kavanagh et al[7] demonstrated a statistically significant increase in household productivity in patients treated with certolizumab pegol. Torii et al evidenced a statistically significant PASI 75 response in patients treated with infliximab.

Conclusions: The evidence shows that TNF-α inhibitors infliximab and certolizumab pegol are effective in treating adults with psoriatic arthritis as well as PsA patients with prior failure of DMARD therapy. They have been shown in these trials to effectively reduce symptoms of arthritis and psoriasis, and improve quality of life with minimal adverse events compared to control. Prompt treatment of PsA with TNF-α inhibitors may impact the disease progression and joint destruction in patients with PsA.

Keywords: Infliximab, certolizumab pegol, TNF-α inhibitors, psoriatic arthritis

INTRODUCTION

Psoriatic arthritis is a spondyloarthropathy occurring in patients with clinical skin or nail psoriasis which leads to progressive and severe destruction of joints. Progressive damage is seen within 2 years by radiographic evidence. Thus, prompt treatment is necessary to control the symptoms of inflammation and progressive damage of articular surfaces.[1] This paper evaluates three randomized control trials comparing the effectiveness of infliximab and certolizumab pegol for the treatment of Psoriatic arthritis.

The estimated incidence is approximately 6 per 100,000 per year with a prevalence of 1 to 2 per 1000 in the general population.[2] The direct estimate for the annual health care costs of PsA in the US is approximately $1.9 billion, with a substantial increase in cost as the disease progresses.[3] In one study, patients with PsA made 20.3 visits to a general practitioner each year and 3.9 visits to a rheumatologist.[3] The precise etiology has not been identified, however, it is known that PsA has a strong genetic component, with approximately 40% of patients with a positive family history of the disease.[4] Tumor necrosis factor (TNF)-α, a pro-inflammatory cytokine, is thought to have a role in the pathogenesis of PsA.[1] Elevated levels of this cytokine has been reported in psoriatic skin lesions as well as in synovial fluid of PsA patients. Interestingly, TNF-α concentration has also been seen to decrease in correlation with increase in therapeutic benefit.[5]

The current goal of treatment is to reduce inflammation and prevent or prolong eventual joint destruction.[6] Choice of initial drug depends on the severity of symptoms and joint disease. Treatment generally consists of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or non-biologic DMARDS such as methotrexate or leflunomide for more moderate disease. However, these drugs produce moderate benefits at best, and the use of TNF-α

inhibitors has generated increased interest as a therapeutic alternative.[1] In addition, the conventional therapies for the treatment of psoriasis in this patient population presents issues of insufficient responses, adverse drug reactions, and recurrence after discontinuation. A novel drug that is effective for psoriasis as well as arthritis is needed.[5] The treatments being proposed are Tumor necrosis factor (TNF) alpha inhibitors, namely infliximab and certolizumab pegol. These agents have been shown to be effective, and are an important treatment option for patients, especially for those who have been refractory to other treatments.

OBJECTIVE

The objective of this selective EBM review is to determine whether "TNF-α inhibitors Infliximab and Certolizumab pegol are effective in treating adults with Psoriatic Arthritis (PsA) or PsA patients who have previously failed disease-modifying anti-rheumatic drug (DMARD) therapy."

METHODS

During the process of this review, three randomized control trials (RCT) were selected. The search criteria consisted of an adult population with or without failure of standard DMARD therapy, infliximab and/or certolizumab pegol as interventions, and outcomes that were patient-oriented. The outcomes chosen were the Psoriasis Area and Severity Index (PASI), Household productivity, and American College of Radiology (ACR) response. The comparisons were chosen against a placebo and from other biologic DMARDs.

The articles were researched through PubMed, using the keywords "TNF-a inhibitors," "infliximab," "certolizumab pegol," and "Psoriatic arthritis." All three articles chosen were based on the relevance to the desired patient population and intervention with patient-oriented outcomes. They were published in English in peer-reviewed journals. Regarding inclusion

criteria, the articles were randomized controlled trials (RCTs), were relevant, and were published within the last 7 years. Non-randomized trials were excluded within reason as well as studies that looked at disease oriented outcomes. The reported statistics included relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), and p-value. A summary of the three articles is provided in table 1.

Table 1: Demographics and Characteristics of Included studies

Study	**Type**	**# Pts.**	**Age (yrs)**	**Inclusion Criteria**	**Exclusion Criteria**	**W/D**	**Interventions**
Atteno[1] (2010)	RCT	100	36-61	Patients older than 18 years old with active PsA and with inadequate response to DMARD therapy	Prior use of TNF inhibitors, usage of more than 10mg of prednisone daily, variation of dosage on NSAIDs or prednisone within 2 weeks of enrollment	0	Infliximab 5mg/kg every 6 weeks
Kavanagh[7] (2015)	RCT	409	35-60	Patients 18 or older with a diagnosis greater than 6 months with active skin lesions or a documented history of psoriasis, prior treatment failure with DMARD	History of inflammatory arthritis other than PsA or secondary condition significant enough to interfere with evaluation, prior treatment with more than two biologics or primary failure to a	40	Certolizumab 400mg at weeks 0,2, 4 followed by either 200mg every 2 weeks or 400mg every 4 weeks subcutaneously with a blinded, pre-filled syringe

					TNF inhibitor.		
Torii[5] (2010)	RCT	54	30-59	PsA patients who have had moderate to severe plaque psoriasis for at least 6 months	History of serious infection, active TB, conventional therapy within 2 weeks before enrollment	7	Induction therapy with Infliximab 5mg/kg IV

OUTCOMES MEASURED

Three outcomes were measured, looking from different perspectives to assess the efficacy of infliximab and/or certolizumab pegol. Atteno et al[1] looked at the American College of Radiology Response (ACR) which accounts for Psoriasis Severity Index (PASI), health assessment questionnaire (HAQ), and tender and swollen joints. Kavanagh et al[7] looked at household productivity, measured by patient survey of symptoms affecting activity. The survey asked every patient the same 5 questions relating to their productivity at home, or lack thereof due to their arthritis: days where no work was performed at home due to arthritis; days where household productivity was reduced by >50%; days with outside hired help due to arthritis; days with leisure activities missed due to arthritis; and level of arthritis interference with household productivity. Torii et al[5] used the Psoriasis Area and Severity Index (PASI), a standardized system based on findings of erythema, induration, and scaling on the head, trunk, and limbs determined on physical exam.

RESULTS

Three randomized control trials were analyzed in this review. All studies evaluated the treatment efficacy of infiliximab (INF) or certolizumab pegol (CZP) over the course of months

for patients greater than 18 years with psoriatic arthritis. Patients who have received prior treatments with TNF-α inhibitors were excluded from the studies.

Atteno et al[1] compared the effectiveness of infliximab (INF) to other TNF-α inhibitors etanercept (ETN) and adalimumab in 100 patients with PsA with inadequate response to a prior DMARD. These patients routinely attended the Psoriatic Arthritis Clinic at the University of Frederico II. The study excluded patients with previous usage of TNF-α inhibitors, and patients who took NSAIDs within 2 weeks and prednisone within 4 weeks, presumably to ensure no overlap between the anti-inflammatory effects of these drugs with the drug of study. Etanercept was chosen as the comparison medicine. The data was presented as dichotomous and all patients were followed with an intention to treat analysis. All patients were randomly given INF 5mg/kg every 6-8 weeks or ETN 50mg weekly. Effectiveness was defined as percentage of ACR 20 responders and as clinical remission. Table 2 demonstrates the status of the patient at the 1 year follow up. Patients treated with INF had higher HAQ scores ($p=0.03$), and less swollen joints ($p<0.01$) than patients treated with ETN at baseline. Additionally, patients receiving INF showed greater improvements of psoriatic rash when compared to ETN ($p <0.01$). ACR response rates were 72% of ETN and 75% of INH. Adverse events, though considered mild to moderate, occurred in 23% of INF patients and 17% of ETN patients ($p<0.01$). There were only two serious adverse effects in the INH group thought to be drug related, pneumonitis and thrombocytopenia. It should be noted that all TNF-α inhibitors effectively controlled signs and symptoms of PsA. Comparing INH to ETN, the relative benefit increase (RBI) was 0.041 and the absolute benefit increase (ABI) was 0.03. The numbers of patients needed to treat (NNT) to achieve desired clinical response was 34.

Table 2: Clinical and therapeutic characteristics of patients after 1 year

	Overall (n=100)	Etanercept (n=36)	Adalimumab (n=34)	Infliximab (n=30)	p value
PASI	0.6 (2)	2 (4.4)	0.1 (1.9)	0 (1)	<0.01
HAQ	0.1 (0.1)	0.1 (0)	0.1 (0.2)	0.1 (0)	0.60
Tender joints	1 (1)	1 (1)	1 (2)	1 (1.8)	0.12
Swollen joints	0 (1)	0 (1)	0.5 (1)	1 (1)	0.23

Kavanagh et al[7] randomized 409 patients age 18 and older who have had PsA for greater than 6 months and prior failure to DMARD therapy. Active psoriatic lesions and increased inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein above upper limits were necessary for consideration of candidates in the trial. Prior treatment with TNF-α inhibitor was allowed in up to 40% of patients. Patients with a secondary non-inflammatory arthritis were excluded due to possible interference with evaluation. Patients were given a loading dose of certolizumab (CZP) 400mg followed by CZP 200mg every 2 weeks or 400mg every 4 weeks. Results were measured by a Work Production Survey which was taken at baseline and every 4 weeks. 90% of the patients completed the 24-week placebo-control, and 43% of the patients who received placebo underwent mandatory escape and were re-randomized. Patients treated with either dose of CZP reported improvements in household productivity and greater participation in leisure activities compared to placebo patients as early as week 4, continuing until week 24. CZP-treated patients reported an average of 3.0-3.5 fewer days with no household work (compared to 1.0; $p<0.05$), 3.6-4.2 fewer days with reduced household productivity (compared to 1.8; $p<0.05$), and PsA interference productivity reduced by 2.3-3.0 (compared to 0.8; $p<0.05$). Additionally, CZP patients also gained an average of 2.3-3.0 days per month for time with family or social activities (compared to 0.9 days; $p<0.05$). Table 3 demonstrates the mean difference and confidence intervals. Notably, days with household work reduced by >50% had a mean difference of 3.9 and 3.4 days for CZP 200mg and CZP 400mg,

respectively with a confidence interval of 95% and p value <0.001. The rates of adverse events, serious adverse events, and infection were similar between CZP and placebo. The most common AEs were diarrhea and headache, with the most common infection being nasopharyngitis. Two deaths occurred during the first 24 weeks; one death in a patient taking CZP 200 caused by myocardial infarction and another death of unknown origin in a patient taking CZP 400. Both deaths were considered unrelated to study medication. Additionally, one patient receiving CZP 400 reported non-invasive cervical carcinoma.

Table 3: Improvements in productivity in the home at week 24.

Productivity at home and daily activities over previous 4 weeks	CZP 200mg – Placebo Mean Diff (95% CI) (p value)	CZP 400mg – Placebo Mean Diff (95% CI)
Days with no household work due to arthritis	-2.3 (-4.0 to -0.7) (0.007)	-2.2 (-3.9 to -0.6) (0.010)
Days with household work reduced by >50%	-3.9 (-5.8 to -2.2) (<0.001)	-3.4 (-5.3 to -1.5) (<0.001)
Days missed of family, social, or leisure activities due to arthritis	-1.7 (-3.1 to -0.5) (0.005)	-1.8 (-3.2 to -0.6) (0.004)
Days with outside help hired due to arthritis	-1.2 (-2.4 to -0.3) (0.008)	-0.4 (-1.7 to 1.0) (0.582)
Rate of arthritis interference with household productivity	-1.8 (-2.5 to -1.2) (<0.001)	-1.5 (-2.1 to -0.8) (<0.001)

Torii et al[5] studied PsA patients with at least moderate to severe plaque psoriasis for at least 6 months. A history of serious infection or active tuberculosis were part of the exclusion criteria due to the immune-suppressing effects of TNF-α inhibitors and possible reactivation of tuberculosis.[8] This phase III multicenter trial was conducted at 28 medical institutes in Japan. It was biphasic and consisted of induction phase through week 14 and a maintenance phase through week 78. The data presented was dichotomous, those reaching PASI 75 response and those who did not. Infliximab was administered over a period of 2 hours on day 0 and at weeks 2 and 6. The maintenance phase was an open label trial to evaluate the efficacy of long term management. In

this phase, infliximab was administered every 8 weeks. A total of 54 patients entered the induction phase. The discontinuation rate was 12.5% in the infliximab group, and 14.9% in the overall population, most commonly due to adverse side effects. Regarding safety and tolerability, there was only one serious adverse event and one adverse drug reaction in both groups with no clear difference. Serious infusion reaction occurred once in the INF group. Only 3 patients had treatment failure and 4 patients dropped out and were treated as "not improved." The PASI response at week 10 was 68.6% in the infliximab group, compared with 0.0% in the placebo group ($p<0.001$). Improvements in PASI 75 rates continued in the maintenance phase through week 66. In the patients receiving placebo who were switched to INF at week 16, the PASI 75 score improved immediately, with a PASI 75 response rate of 66.7% at week 26 (as demonstrated in figure 1). The absolute benefit increase (ABI) was 0.686 and the number of patients needed to treat (NNT) to achieve a PASI 75 response was 2 patients.

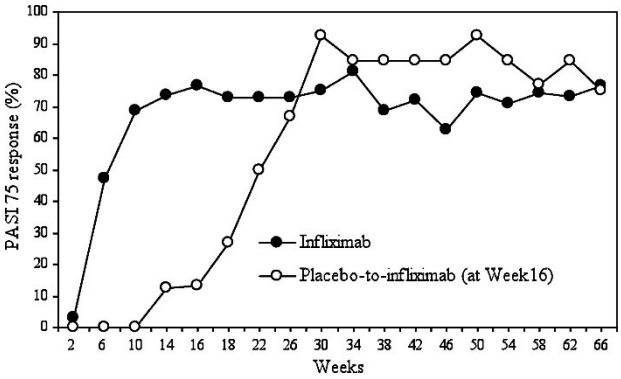

Figure 1: Percent of patients achieving PASI 75 response from baseline through week 66.

DISCUSSION

Psoriatic arthritis is a chronic inflammatory arthritis seen in 30% of patients with psoriasis. A substantial proportion of these patients will progress in disease severity until functional impairment, sometimes leading to work disability and loss of productivity with associated decreased quality of life.[1] Current regimes have been less than ideal, and a novel

agent is needed to treat both the symptoms and severity of joint inflammation as well as psoriatic skin lesions.

Infliximab (Brand name: Remicade) is a chimeric monoclonal antibody that binds TNF-α and thus reducing levels of TNF-α in tissue of fluids of patients with psoriatic arthritis as well as other inflammatory diseases.[9] It is also used to treat patients with ankylosing spondylitis, inflammatory bowel disease, and rheumatoid arthritis. FDA warnings for this drug include increased risk of serious infection, increased risk of cancer (specifically Lymphoma in children), and reactivation of latent tuberculosis.[9] The cost for this drug is approximately $1400 for a 100mg reconstituted solution.[9]

This systematic review analyzed three randomized control trials which demonstrated the effectiveness of infliximab and certolizumab pegol in the treatment of PsA.[1,5,7] Atteno et al[1] showed that infliximab significantly reduces the number of tender and swollen joints as well as psoriasis severity which is reflected in their increased value of their own health assessment. Kavanagh et al[7] found that patients treated with certolizumab pegol greatly affected the patient's productivity in the home. Patients gained more days of productivity, experienced less interference from arthritis with their activities at home, and were able to spend more time in leisure activities or time with friends and family. Torii et al[5] found that infliximab showed sustained improvement of joint and skin symptoms correlating with increase quality of life and is useful for the treatment of PsA.

Regarding limitations, Atteno et al[1] only studied 100 patients which is a small sample size, and may not be indicative of the population at large. A significant limitation in the Kavanagh et al[7] study was the use of Last Observation Carried Forward in the 10% of patients that were lost to follow-up to impute missing data. In 2012, the National Research Council's

Panel on Handling Missing Data in Clinical Trials recommended against the use of this method due to demonstrated inaccuracies, and any data analysis using this method should be questioned for validity.[10] Finally, a potential limitation in the Torii et al[5] study is that the study took place across 28 medical institutes in Japan, outside of the oversight, standards, and regulations of the United States.

CONCLUSION

The evidence shows that TNF-α inhibitors infliximab and certolizumab pegol are effective in treating adults with psoriatic arthritis as well as PsA patients with prior failure of DMARD therapy. They have been shown in these trials to effectively reduce symptoms of arthritis and psoriasis, and improve quality of life with minimal adverse events compared to control.[1,5,7] Prompt treatment of PsA with TNF-α inhibitors may impact the disease progression and joint destruction in patients with PsA.

While these drugs have been shown to be efficacious, autoantibody formation to TNF-α inhibitors during treatment is an area of concern. The presence of anti-nuclear antibodies and anti-double-stranded DNA antibodies have been seen and has been associated with autoimmune phenomena such as lupus-like syndrome or demyelination.[12] Although the exact mechanism and clinical implications require clarification, reports have linked this autoantibody formation to undesirable clinical manifestations.[12] Future research should determine the extent and prevalence of this phenomenon.

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