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TNF-α Antagonists in the Treatment of Nail Psoriasis

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Abstract

Background: Nail psoriasis affects approximately 50% of psoriasis patients and in many cases causes functional impairment in manual dexterity, pain and psychological stress. It is often overlooked, not treated effectively. Physicians often believe that the condition is difficult to treat. The risks of systemic conventional therapy are not justified and the difficulty of delivering effective topical drugs to the nail unit is a big challenge for physicians. Hence many psoriasis patients do not receive an effective treatment for nail disease. Recently, systemic therapy with biologic agents targeted against tumour necrosis factor alpha (TNF-α) has found a place in the management of psoriasis and psoriatic arthritis, and their effects on nail psoriasis have been investigated. The aim of this article is to evaluate the response of nail psoriasis to biological agents and compare the effectiveness of three different TNF-α antagonists (infliximab, adalimumab and etanercept).

Introduction

Psoriasis is a chronic inflammatory skin disease affecting approximately 1.5-3% of the world population [1]. Three biologic agents are currently licensed in the Turkey for the treatment of moderate-to-severe psoriasis (adalimumab, etanercept, and infliximab). Although skin lesions are the most common clinical findings in psoriasis, almost half of the patients show nail involvement; the incidence of life-long nail involvement has increased to 80-90% [2]. In patients with psoriatic arthritis, the rate of the nail involvement rises up to 75-86% [3]. On the other hand nail findings present as the only symptom in less than 5% of patients. Nail involvement is found in men 10% more than women and it is positively correlated with high body weight [4].

In many cases the presence of nail involvement causes functional impairment of manual dexterity, pain and psychological stress, placing a significant burden on the patient's quality of life [2, 5]. Nail involvement in psoriasis may be a predictor of future inflammatory joint damage, a precursor to psoriatic arthritis, and a visible indicator of disease activity. On the contrary, nail psoriasis is often overlooked by clinicians and not treated effectively. The risks of systemic conventional therapy are not justified and the difficulty of delivering effective topical drugs to the nail unit are big challenges for physicians. Hence many psoriasis patients do not receive an effective treatment for nail disease [2, 4].

Recently, systemic therapy with biologic agents targeted against tumour necrosis factor alpha (TNF-α) has found a place in the management of psoriasis and psoriatic arthritis, and their effects on nail psoriasis have been investigated. The aim of this article is to evaluate the response of nail psoriasis to biological therapy and compare the effectiveness

of three different TNF-α antagonists (infliximab, adalimumab and etanercept).

Infliximab

Infliximab is an intravenously administered, chimeric (rodent-human) IgG1 anti-TNF-α antibody. It binds with a high affinity and specificity to TNF-α and neutralizes its biological activity. Infusions of 5mg/kg are performed at weeks 0, 2 and 6 initially. And then maintenance therapy is usually performed every 8 weeks. Infliximab was approved by the U.S. Food and Drug Administration (FDA) for the treatment of psoriasis, *Crohn*'s disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis. Infliximab won its initial approval by the FDA for the treatment of Crohn's disease in August 1998. According to product labeling, infliximab neutralizes the biological activity of TNF-α by binding with high affinity to the soluble and transmembrane forms of TNF-α, and inhibits or prevents the effective binding of TNF-α with its receptors. Additionally, infliximab has the capability of lysing cells involved in the inflammatory process [**6**].

Although it is shown that all the biological agents have various effects on treating nail psoriasis, the most comprehensive and robust data are available for infliximab [**2**]. To evaluate the long term efficacy and safety of infliximab in moderate- severe plaque psoriasis, phase III multicentered double-blind randomized controlled study (EXPRESS) was performed involving 378 patients randomly assigned in a 4:1 ratio to receive infliximab 5 mg/kg at weeks 0, 2, 6 and every 8 weeks through to week 46 (n=301), or placebo at weeks 0, 2, 6, 14 and 22, then crossing over to infliximab at weeks 24, 26, 30, 38 and 46 (n=77). Nail psoriasis was present in 240 patients of the infliximab group and in 65 of the placebo group. Mean percentage improvements in nail psoriasis severity index (NAPSI) score at weeks 10 and 24 were 26.8 and 57.2%, respectively in the infliximab group versus -7.7% and -4.1%, respectively, in the placebo group. Infliximab resulted in complete clearing of nail psoriasis 6.9% of patients within 10 weeks, rising to 26.4% after 24 weeks, and 44.7% after 50 weeks. In placebo recipients, nail clearence was observed in 1.7% and 5.1% of patients at weeks 10 and 24, but this increased to 34.5% at week 38 and to 48.2% at week 50 after the patients had switched to infliximab. In this study it is shown that infliximab has a rapid onset and long lasting effect with complete clearance in almost half of treated patients [**4, 7, 8**].

There are also small similar studies support the efficacy of infliximab in the literature . Infliximab was shown to be effective at a study, published by *Rigopoulus* et al., in 18 psoriasis patients with nail involvement in 2008. The response to treatment was assessed at baseline and at weeks 14, 22, 30, 38 using NAPSI and Life Quality Index before and after the treatment. Significant improvement was seen in most patients after the third infusion as shown by the reduction of mean NAPSI from 55.8 at baseline to 29.8 at week 14. After six infusions, at the 38 weeks, almost complete resolution had observed in nail involvement and the mean NAPSI score was found 3.3.

Significant improvement was found in patients' quality of life with reduction of the score of the international quality of life questionnaire from 66.3 at baseline to19.1 at week 38 (In life quality index scale 0 representing the best, and 100 representing the worst quality of life). Amelioration of both matrix and nail bed psoriatic signs in the patients treated with infliximab suggests its wide therapeutic potential. Although there are no comparative studies, infliximab may be safer and more effective than traditional systemic therapies, based on outcomes from studies with retinoids, cyclosporin, methotrexate and PUVA. No adverse event was observed during the treatment [**9**].

Fabroni et al. evaluated the efficacy of infliximab retrospectively in 48 patients with moderate- severe plaque psoriasis and psoriatic arthritis accompanied by nail involvement. The NAPSI scores of patients at weeks 0, 14, 22, 38 and percentage of patients achieving NAPSI -50,-75,-90 at 14, 22 and 38 weeks were calculated. In most cases a rapid nail improvement was observed after 22 weeks of infliximab therapy, but a complete nail clearing was reached in only five (10.4%) patients. Moreover, of 48 patients treated with infliximab, NAPSI-50 was not achieved in only one patient after 38 weeks after starting the treatment, demonstrating a low frequency of non-responders to infliximab. There are some limitations

in this study. They do not have data of follow up longer than 38 weeks to assess long-term efficacy of this treatment in nail psoriasis [**10**].

Adalimumab

TNF-α inactivation has proven to be important in downregulating the inflammatory reactions associated with autoimmune diseases. As of 2008 adalimumab has been approved by the FDA for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, g's disease, moderate to severe chronic psoriasis, and juvenile idiopathic arthritis. Adalimumab is a recombinant, human, IgG1 monoclonal antibody specific for tumor necrosis factor. Adalimumab is a fully human anti-TNF-α antibody that is self injected subcutaneously at a dosage of 40 mg every 2 weeks for psoriasis and psoriatic arthritis. In the multinational, open-label Safety and Efficacy Study of Adalimumab in Patients with Active Psoriatic Arthritis (STEREO) in 442 patients, 259 of whom had nail involvement, mean NAPSI scores improved with adalimumab treatment from 20.6 at baseline to 11.5 at week 12 and 7.3 at week 20. In the mean NAPSI score, approximately 45% decrease was detected at the end of the 12th week and 65% decrease was detected at the end of the 20th week. The improvements in NAPSI score were independent of other skin change assessment measures, and occured regardless of joint response status [**11**].

Rigopoulos et al. found a striking amelioration at the end of the treatment in a total of 21 patients with nail involvement, seven of which had serious plaque psoriasis and fourteen of them having psoriatic arthritis, in a study assessing the efficacy of adalimumab in nail psoriasis. Treatment response was evaluated via NAPSI scores at the beginning of the treatment and at the end of 12^{th} and 24^{th} week. Improvement was evident as early as week 12 for both fingernails and toenails. Significant improvement was recorded after the eight injection. The value of NAPSI score in fingernails was reduced from 10.57 to 1.57 in patients with plaque psoriasis and from 23.86 to 3.23 in patients with psoriatic arthritis. The absence of a control group was one of the restrictive aspects of the study [**12**].

There are also few case reports mentioning the efficacy of adalimumab in nail psoriasis. *Irla* and *Yawalkar* revealed a significant improvement in two cases with nail psoriasis, unresponsive to topical and traditional systemic treatments. The first case was 36-year-old male with severe plaque psoriasis and psoriatic nail dystrophy in all finger and toe nails. Complete resolution of the lesions on his finger nails was seen within 3-4 months of treatment and marked improvement in his toe nails after 7 months of therapy. Adalimumab was discontinued after 7 months, because the patient did not want continue. His cutaneous and nail psoriasis relapsed within 4 months after the treatment had been stopped. A retreatment with adalimumab induced reimprovement and complete remission of the lesions on his finger nails together with a marked improvement in his toe nails was found after 5 months. The second patient with severe nail psorisis was a 46-year-old male patient with a history of plaque psoriasis and psoriatic arthritis. The patient, unresponsive to topical and systemic treatments was started adalimumab therapy with a loading dose of 80 mg followed by a dose of 40 mg administered subcutaneously once in two weeks. Complete resolution of his nail involvement was observed after 8 months of treatment. Afterward, the patient want to stop the treatment and has remained clear of disease especially finger nails for 8 months after stopping the therapy [**13**].

Etanercept

Etanercept is a recombinant human TNF receptor fusion protein that binds to TNF-α with greater affinity than its natural receptors. The bound TNF-α is biologically inactive. After the initialization dose of 50 mg twice a week for 12 weeks, it is usually applied 50 mg once a week or 25 mg twice a week subcutaneously as the maintenance therapy [**14**].

In the CRYSTEL study, including 546 patients with moderate-severe plaque psoriasis with nail involvement, the patients were treated continuously or intermittently for 54 weeks in order to evaluate the effectiveness of etanercept on nail psoriasis. Patients were divided randomly to receive continuous etanercept therapy administered as 25 mg sc twice

weekly throughout the 54 week study or paused etanercept therapy initiated at a dose of 50 mg sc twice weekly and continued for a maximum of 12 weeks until the target response was achieved. If the patients experienced a relapse, the treatment was continued subcutaneously twice a week at a dose of 25 mg until response to treatment was achieved. Then, the treatment was again discontinued. The same treatment scheme was applied on relapses during treatment. Nail psoriasis was assessed using NAPSI at baseline and at12, 24, 36, 54. weeks or at the time of discontinuation. The NAPSI scores of all the patients decreased by an average of 28.9% at the end of 12. week and 51% at 54. week. Nail lesions totally disappeared in 30% of patients at the end of 54th week [**8, 15**].

A randomized double-blind placebo controlled study by *Pariser* et al. including 34 children and adolescent with severe plaque psoriasis and nail involvement receiving continuous etanercept (n=12) or placebo (n=22) showed 36% decrease in NAPSI score at week 12 with etanercept compared with 0.1% for those receiving placebo. Thereafter, etanercept treatment was given to all groups for the next 24 weeks. The mean percentage reduction in NAPSI score from baseline was 47% for patients taking etanercept for 36 weeks and 67% for patients initially taking placebo followed by 24 weeks of etanercept treatment [**8**].

In a double-blind, placebo-controlled study in patients with moderate to severe plaque psoriasis with nail psoriasis received etanercept 50mg BIW or placebo BIW subcutaneously in a blinded fashion for 3 months. A total of 58 patients (31 in the etanercept group and 27 in the placebo group) had photographs available for scoring at both baseline and month 3. At baseline, the mean photo derived NAPSI score was 49.2 in the etanercept group and 50.7 in the placebo group. There was clinically meaningful mean improvement in the NAPSI score of 8.6 at 3 months in the etanercept group, as compared with a worsening NAPSI score of -3.0 in the placebo group [**6, 16**].

In another retrospective study 66 patients with psoriasis treated with etanercept intermittently and followed up for nearly 3.5 years. Etanercept was effective during all treatment cycles but statistically significant improvement was observed at the first two cycles [**17**].

There are similiar case reports showing the rapid clinical improvement and marked amelioration on etanercept treatment in patients unresponsive to traditional systemic treatments and severe nail involvement [**18, 19**].

In literature there are few compereative studies about these three biological agents.

Seraceno et al. assessed the efficacy of biological agents in nail psoriasis in a prospective study allocated TNF inhibitor treatment for psoriasis or psoriatic arthritis with severe nail involvement (NAPSI > 14) to consecutive patients: 14 patients received adalimumab, 14 received etanercept and 14 received infliximab. Response to the treatment evaluated by NAPSI scores at 0, 2, 6, 14, 16, 22. weeks. At week 6, there was a 28% reduction in NAPSI score in the adalimumab-treated group, 56% in the etanercept-treated group and 63% in the infliximab-treated group. Infliximab was the only agent to achieve a significant reduction in NAPSI score at week 6. There was no significant decrease detected in NAPSI score in the etanercept and adalimumab groups until 22th week. At week 22, the NAPSI score reductions 64%, 65%, 89% for etanercept, adalimumab and infliximab respectively. These datas show that infliximab is the most effective and it has a more rapid onset of action than either adalimumab or etanercept [**8, 20**]. In another study the reduction in NAPSI score was found to be significantly higher in 12th and 24th weeks of treatment with infliximab and adalimumab, while this difference was no longer present in the 48th week of treatment [**21**].

According to the evaluation of 11 physicians specialised in the psoriasis field, all participants share the same idea that infliximab has the most robust activity in the treatment of skin and nail psoriasis in comparison to other biological agents. The second best treatment agent was thought to be adalimumab. 6 of the participants chose adalimumab, 3 of them chose etanercept and 2 of them chose ustekinumab as the second line treatment agent [**2**].

As a corollary; although infliximab therapy seems to be superior to the other biological agents as it provides a rapid start of the action and a marked clinical improvement in the treatment of nail psoriasis, there are also existing publications that in long term there is no marked difference among these three agents. Long term research projects with higher participation rate comparing the efficacy of these agents are needed.

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