Comparing the effectiveness of adalimumab and etanercept on nail lesions in patients with psoriatic arthritis; a prospective longitudinal study

Amin Dadfar, Elham Rajaei, Alireza Ghanbaran, Nader Paziar

Abstract

**Introduction**: Nail involvement occurs in about 80% of patients with psoriatic arthritis, and it can seriously affect the quality of life. Up to now, there is no evidence about which biological drug is the most effective on nail lesions in our country.

**Objectives**: The aim of this study was to compare the effectiveness of two well-known biological drugs in our country, adalimumab and etanercept, on nail lesions of psoriatic arthritis.

**Patients and Methods**: A prospective longitudinal study conducted on psoriatic arthritis patients with nail lesions referred to the Golestan hospital in Ahvaz from 2020 to 2022. A total of 57 patients in two groups of receiving adalimumab (CinnoRA 40 mg; n=28) and etanercept (Altebrel 50 mg; n=29) for 12 weeks. Clinical response and characteristics of nail lesions were evaluated with Nail Psoriasis Severity Index (NAPSI) and Lesion Quadrant Index (LQI) at baseline and after 12 weeks.

**Results**: There was a statistically significant improvement in LQI and NAPSI scores after 12-week treatment with etanercept and adalimumab. However, after the treatment, there was no significant difference in median of NAPSI of (P=0.685) and LQI (P=0.779) between the two groups etanercept and adalimumab. The complete improvement of NAPSI score with etanercept and adalimumab after 12 weeks was observed in 14 patients (48.3%) in etanercept group and 11 patients (39.3%) in adalimumab group (P=0.494). No adverse effects were observed as well.

**Conclusion**: Etanercept and adalimumab have been shown to ameliorate nail lesions in psoriatic arthritis during 12 weeks. However, the effectiveness of etanercept and adalimumab in improving nail lesions in psoriatic arthritis patients was similar.

Keywords: Nail psoriatic arthritis, Etanercept, Adalimumab, NAPSI score, Lesion quadrant index

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**Key point**

The prospective study compared the effectiveness of two biological drugs, adalimumab and etanercept, in treating nail lesions in patients with psoriatic arthritis. The study found that 12-week treatment with both drugs improved nail lesions. However, there was not a statistically significant difference in nail lesions improvement (reduction of NAPSI and LQI scores) between etanercept and adalimumab.

Nail Psoriasis Severity Index (NAPSI) is a numeric graded system for nail involvement and is universally used in clinical practice. We believe that the NAPSI score system can be helpful in comparing biological medications. Each nail is divided into four quadrants and graded from to four (one point for each quadrant). In this way, a matrix score (0-4) and bed score (0-4) are obtained, with a maximum of 8 for each nail. The sum of the scores give the total NAPSI
score for all fingernails (0-80) (4). In our study, bed lesions of nail included onycholysis, hyperkeratosis, oil spot, and discoloration of the nail, and similarly, matrix lesions of nail included pitting and leukonychia.

The Lesion Quadrant Index (LQI) is another grading system similarly to the NAPSI score that each nail is divided into four quadrants with the differences being the counting of nail lesions is conducted without considering the number of fingernail and types of nail lesions (bed or matrix lesions) and it shows the location of involvement in the nail corresponding quadrants (4).

Treating nail psoriasis is often a time-consuming challenge with an insecure outcome. as the nail apparatus limits the absorption of many topical drugs. Patients usually report improvement in their nail lesions when they start systemic treatment for their skin or joint psoriatic lesions. Traditional therapies for nail lesions include methotrexate, cyclosporine and corticosteroids. Currently, we know a series of mechanisms that can lead to flare-ups of psoriatic disease and it causes psoriatic complications such as nail lesions and arthritis. Among these mechanisms, cytokines, especially tumor necrosis factor (TNF) α and β, as well as interleukin (IL)-12 and IL-23, play an important role. Therefore, biological therapies especially anti-TNF drugs, improve symptoms and outcome of patients and their complications such as nail lesions (5,6).

Objectives
Few studies have assessed the behavior of nail lesions in patients who received biological therapies. There is limited evidence about which anti-TNF drugs are more effective for the treatment of nail involvement in psoriatic arthritis. We focused on two significant anti-TNF drugs approved in our country, namely adalimumab (CinnoRA) and etanercept (Altebrel). Therefore, we compared the effectiveness of these two drugs on nail lesions of psoriatic arthritis in our country.

Patients and Methods
Study design
This prospective longitudinal study conducted on psoriatic arthritis patients with nail lesions referred to the Golestan hospital in Ahvaz from 2020 to 2022.

Evaluations
Although no standard global measurement system for nail lesions has been validated currently, the NAPSI score is usually used in clinical investigations, and we utilized it in the present study. We also proposed a counting system called the LQI. We believe that both the NAPSI score and the LQI can be helpful in comparing biological medications.

Participations
Patients were selected by the available sampling method (non-randomized) and, based on the inclusion and exclusion criteria as follows:

Inclusion criteria included patients diagnosed with psoriatic arthritis based on the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria; Patients with nail involvement as determined by clinical examination; and initiation of treatment with anti-TNF drugs after the start of the study (7).

Exclusion criteria included age below 17 years; Receipt of any other treatment for nail lesions associated with psoriatic arthritis within 8 weeks prior to the start of the study; Presence of concomitant nail diseases, such as onychomycosis or other nail infections; Other rheumatologic diseases that could interfere with the evaluation of the study outcomes; Pregnancy or breastfeeding; and History of any malignancy, demyelinating diseases, or congestive heart failure of New York Heart Association class 3 or 4, which had a contraindication for the use of anti-TNF drugs.

Accordingly, a total of 57 patients were eligible, which included in two groups receiving CinnoRA (adalimumab 40 mg; n = 28) or Altebrel (etanercept 50 mg; n = 29) once a week for 12 weeks. Prescription medications were as the routine treatment which administered by a specialist. All clinical and demographic information was extracted from the patients’ medical records. To reduce the bias of the study, we tried to select patients who were as similar as possible in terms of the severity of disease (being active or inactive) and history of taking medications, such as glucocorticoids and disease-modifying antirheumatic drugs (DMARDs).

Patients' evaluation
All patients were visited regularly to evaluated the effectiveness of the treatment. Clinical response and characteristics of nail lesions at baseline and 12 weeks after treatment were assessed using the NAPSI and the LQI. All evaluations were conducted by a single physician. Some patients who were unable to come to the clinic for follow-up visits were recommended to take photographs of their fingernails instead and send them for quality assessment. As an efficacy endpoint, we compared the number of patients with 100% NAPSI reduction (complete improvement of nail lesions) after 12 weeks between the two groups.

Statistical analysis
Normality of variables was assessed using the Kolmogorov–Smirnov test. Data that follows a normal distribution is displayed as mean ± standard deviations, whereas non-normally distributed data is represented by the median (Interquartile range). Categorical variables are expressed as frequency (percentage). Comparisons of continuous variables between two groups were conducted by using independent samples t-test (or nonparametric Mann–Whitney U test) as appropriate. Differences between categorical variables were assessed with a chi-square test.
Nail lesions in psoriatic arthritis

The nonparametric Wilcoxon signed-rank test was used to compare the difference between pairs measurements. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24.0 (SPSS Inc., IBM, Chicago, IL, USA) and a P value of < 0.05 was considered statistically significant.

Results
A total of 57 patients with psoriatic arthritis affected by nail lesions who received biological therapy were divided into two groups of received etanercept (n = 29) or adalimumab (n = 28). The mean age of patients was 32.53±9.50 (between 17-51) years and were including of 30 females (52.6%) and 27 males (47.4%).

There were no significant differences between the two groups in terms of age, gender, body mass index, duration of the psoriatic arthritis disease, inflammatory factors, different of nail lesions, and dosage and method of methotrexate used (Table 1). The frequency of hyperkeratosis, and onycholysis were the highest at 49.1% and 43.9%, respectively, and the frequency of leukonychia and discoloration were the lowest at 15.8% for each one.

Both indexes of LQL and NAPSI decreased significantly in both groups after 12-week treatment (P<0.0001). However, after the treatment, there was no significant difference in median of NAPSI of (P = 0.685) and LQL (P = 0.779) between the two groups etanercept and adalimumab (Tables 2 and 3).

The complete improvement of psoriatic nail involvements (100% reduction in LQL and NAPSI after 12-week treatment) was observed in 14 patients (48.3%) in etanercept group and 11 patients (39.3%) in adalimumab group (P = 0.494). No adverse effects were observed. There was not found any statistically significant relationship between reduction in NAPSI and LQI scores with age (P = 0.576 and P = 0.598 respectively) and gender (P = 0.219 and P = 0.294 respectively) and types of nail lesions (P > 0.05 in all comparisons).

Discussion
Nail involvements are a common feature of psoriatic arthritis and lead to notable impairment in quality of life. Despite recent developments in the treatment of psoriatic arthritis, the management options of nail psoriatic arthritis remain fairly limited, and treating nail lesions continues to be a challenge for physicians (5). The current study was a prospective, longitudinal evaluation on the patients with nail psoriatic arthritis. Moreover, considering the potential role of biological treatments, we decided to assess the effectiveness of two significant drugs, Adalimumab and Etanercept, on the nail lesions of psoriatic arthritis. In this context, several studies have attempted to compare the effectiveness of these drugs on nail involvement.

In terms of drug response in different studies, results have been varied and somewhat controversial. Few studies have compared the efficacy of biological treatment on nail psoriatic arthritis based on subjective and objective methods which was accepted by most researchers. A few studies were evaluated the effectiveness of Adalimumab in treating nail psoriatic arthritis. We will mention some of them and discuss them.

In the study by Van den Bosch et al, on 442 patients with psoriatic arthritis who received adalimumab reported a reduction in NAPSI score after 12 and 20 weeks by 57% and

Table 1. Basic characteristics of patients in two groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Total</th>
<th>Altebral (n=29)</th>
<th>CinnoRA (n=28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year), mean±SD</td>
<td></td>
<td>32.53±9.50</td>
<td>31.97±9.35</td>
<td>33.11±8.79</td>
<td>0.654*</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Female</td>
<td>30 (52.6)</td>
<td>16 (55.2)</td>
<td>14 (50.0)</td>
<td>0.696*</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>27 (47.4)</td>
<td>13 (44.8)</td>
<td>14 (50.0)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td></td>
<td>27.42±3.21</td>
<td>27.46±3.22</td>
<td>27.39±3.25</td>
<td>0.936**</td>
</tr>
<tr>
<td>Duration of disease (month), mean ± SD</td>
<td>27.21±18.94</td>
<td>25.52±18.38</td>
<td>28.96±19.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/h), mean ± SD</td>
<td></td>
<td>30.26±13.97</td>
<td>31.79±16.47</td>
<td>26.60±9.83</td>
<td>0.051*</td>
</tr>
<tr>
<td>CRP (mg/L), mean ± SD</td>
<td></td>
<td>8.62±8.59</td>
<td>9.57±7.88</td>
<td>7.60±10.03</td>
<td>0.451*</td>
</tr>
<tr>
<td>Nail lesions, n (%)</td>
<td>Hyperkeratosis</td>
<td>28 (49.1)</td>
<td>12 (41.4)</td>
<td>16 (57.1)</td>
<td>0.234*</td>
</tr>
<tr>
<td></td>
<td>Onycholysis</td>
<td>25 (43.9)</td>
<td>14 (48.3)</td>
<td>11 (39.3)</td>
<td>0.494*</td>
</tr>
<tr>
<td></td>
<td>Nail pitting</td>
<td>21 (38.8)</td>
<td>12 (41.4)</td>
<td>9 (32.1)</td>
<td>0.470**</td>
</tr>
<tr>
<td></td>
<td>Oil spot</td>
<td>19 (33.3)</td>
<td>10 (34.5)</td>
<td>9 (32.1)</td>
<td>0.851*</td>
</tr>
<tr>
<td></td>
<td>Discoloration</td>
<td>9 (15.8)</td>
<td>5 (17.2)</td>
<td>4 (14.3)</td>
<td>0.760*</td>
</tr>
<tr>
<td></td>
<td>Leukonychia</td>
<td>9 (15.8)</td>
<td>6 (20.7)</td>
<td>3 (10.7)</td>
<td>0.320*</td>
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<tr>
<td>Methotrexate dosage (mg), mean ± SD</td>
<td>16.66±3.81</td>
<td>16.37±3.98</td>
<td>16.96±3.67</td>
<td>0.568*</td>
<td></td>
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<tr>
<td>Methotrexate, n (%)</td>
<td>IV</td>
<td>21 (46.8)</td>
<td>9 (31.0)</td>
<td>12 (42.9)</td>
<td>0.355**</td>
</tr>
<tr>
<td></td>
<td>Orally</td>
<td>36 (63.2)</td>
<td>20 (69.0)</td>
<td>16 (57.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, Body mass index; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein.
* Independent samples t-test; ** Chi-square test.
Table 2. NAPSI before and after treatment in Altebrel (etanercept) and CinnoRA (adalimumab) groups

<table>
<thead>
<tr>
<th></th>
<th>Altebrel (n=29)</th>
<th>CinnoRA (n=28)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20 (20-30)</td>
<td>6 (4-19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 12</td>
<td>2 (0-10)</td>
<td>2 (0-8.75)</td>
<td>0.685a</td>
</tr>
<tr>
<td>% Reduction</td>
<td>75.0 (66.67-100)</td>
<td>66.67 (50.0-100)</td>
<td>0.087a</td>
</tr>
</tbody>
</table>

Abbreviation: NAPSI, Nail Psoriasis Severity Index. Data are expressed as Median (25th–75th percentile).
* Mann-Whitney U test; ** Wilcoxon signed-rank test.

Table 3. LQI before and after treatment in Altebrel (etanercept) and CinnoRA (adalimumab) groups

<table>
<thead>
<tr>
<th></th>
<th>Altebrel (n=29)</th>
<th>CinnoRA (n=28)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2 (2-3)</td>
<td>2 (1-3)</td>
<td>0.108a</td>
</tr>
<tr>
<td>Week 12</td>
<td>1 (0-1)</td>
<td>1 (0-1)</td>
<td>0.779a</td>
</tr>
<tr>
<td>% Reduction</td>
<td>77.01 (68-100)</td>
<td>71.42 (62.0-100)</td>
<td>0.296a</td>
</tr>
</tbody>
</table>

Abbreviation: LQI, Lesion Quadrant Index. Data are expressed as Median (25th–75th percentile).
* Mann-Whitney U test; ** Wilcoxon signed-rank test.

91%, respectively (8). The study conducted by Rudwaleit et al, on 223 patients with psoriatic arthritis showed that after receiving Adalimumab every 2 weeks, the NAPSI score was reduced at 12 weeks by 33% (9). Previously, Leonardi et al showed that after receiving adalimumab and placebo in psoriatic patients, NAPSI score was reduced at 16 weeks by 50% and 8%, respectively (10). In another study in patients with psoriatic arthritis, treatment with adalimumab was able to reduce NAPSI score after 12 and 24 weeks by 46% and 86%, respectively (11). The study conducted by Saraceno et al, on 20 psoriatic patients who received adalimumab and etanercept showed a reduction in NAPSI score at 12 weeks by 37% and 32%, respectively (12). In 2013, another study conducted by Al-Mutairi et al, on psoriatic patients who received Etanercept and adalimumab showed a reduction in NAPSI score at 24 weeks by 68% and 71%, respectively (13). In another study conducted by Bardazzi et al, on psoriatic patients who received etanercept and adalimumab reported a reduction in NAPSI score at 12 weeks by 62% and 66%, respectively (14). Therefore, the finding of these studies showed that adalimumab was as effective as etanercept to improve nail lesions in psoriasis arthritis, and the findings of the present study support these results.

Barrera et al retrospectively conducted as study on psoriatic patients, who received etanercept bi-weekly for 24 weeks. They found a significant improvement in the appearance of nail lesions after less than 12 weeks (15). A rapid improvement was also reported in another study by Rallis et al following the treatment by etanercept in psoriatic patients who were refractory to other treatments (16). Moreover, in a retrospective study by Kyriakou et al, on psoriatic patients after receiving etanercept and adalimumab showed a reduction in NAPSI score at 12 weeks by 42% and 36%, respectively (17). These results in terms of the relative similarity of the effectiveness of the two medicines are in line with the findings of our research. Accordingly, in the study by Ozmen et al, on 17 psoriatic patients who received etanercept and adalimumab showed a reduction in NAPSI score at 48 weeks by 58% and 54%, respectively (18). Likewise, the study by Bissonnette et al, on psoriatic patients showed a reduction in NAPSI score at 12 and 24 weeks by 38% and 35%, respectively (19). In another study, rapid improvement has also been reported with etanercept in a patient who had been refractory to other treatments (20). In another study, nine patients with psoriasis who have received etanercept showed a reduction in NAPSI score at 12 and 24 weeks by 24% and 68%, respectively (21). In a recent study that compared biological drugs in patients with nail psoriasis, adalimumab was superior (22). In these studies, etanercept has proved more efficacy as individually or in comparison with adalimumab. Our results also support the effectiveness of etanercept for treating psoriasis of the nails, although its effect was not significantly better than adalimumab. In our study, 48.3% patients received etanercept once a week, and 39.3% of patients who received adalimumab were achieved NAPSI 100% after 12 weeks.

Notably, the study by Ortonne et al on psoriatic patients who had received etanercept in two forms, once a week and twice a week. They reported complete improvement in nail lesions (NAPSI 100%) at 24 weeks by 31% and 14% of patients, respectively. Therefore, it has proved more efficacy with etanercept if it administered as once a week (23). In another study, Luger et al, assessed 562 patients with psoriasis. In that trial, 66% of the patients who had nail lesions and arthritis treated with etanercept three times a week. It reported a significance reduction in NAPSI score at 12 and 54 weeks by 29% and 51%, respectively. Moreover, after 54 weeks, 30% of patients achieved NAPSI 100% (24). It showed that, the percentage of complete recovery of nail lesions in our study was more than both studies and the patients achieved NAPSI 100% in shorter time (12 weeks).

According to recent studies, etanercept had more efficacy on nail psoriasis than cutaneous psoriasis and arthritis and also if skin and joint involvement were predominant, adalimumab was the more effective one (25,26).

Another interesting finding was that the improvement of nail lesions did not depend on the type of the involvement (matrix, bed, or mixed); therefore, none of the types of nail lesions separately had not a statistically significant relationship with the response to adalimumab or etanercept (21). Our results also support this subject.

Although in the study of Ortonne et al, nail psoriasis had more severity in men and in patients who had a higher BMI, however the gender of participants was not an effective factor in the improvement of nail lesions (23). Similarly, in our study, the gender of patients was not an
important factor. Although more studies were showed a higher percentage of nail matrix lesions and pitting in psoriatic patients (27,28), since in our study, bed lesions like hyperkeratosis and onycholysis were the most frequent lesions.

In our study, patients were well satisfied with receiving the drugs and except for few patients who had erythema at the injection site and local sensitivity, no specific side effect was not reported in the process of treatment.

**Conclusion**
To the best of our knowledge, it was the first study in our country to evaluate the efficacy of biological therapies, including adalimumab and etanercept, in treatment of nail psoriatic arthritis. We found that after 12 weeks treatment with either etanercept or adalimumab there was a clinically significant improvement in nail lesions of psoriatic arthritis, as measured by the NAPSI and LQI scores. Although, the improvement in nail psoriatic arthritis in the etanercept group was slightly greater than the adalimumab group, but this was not statistically significant. It could be concluding that 12-week treatment with etanercept and adalimumab results in similar improvement of nail lesions in patients with psoriatic arthritis.

**Limitations of the study**
One of the limitations of our study was the lack of consistent patient cooperation with scheduled weekly visits. To mitigate this, we offered free, unscheduled visits outside of regular appointments and encouraged patients to submit photographic documentation of their nail lesions. Another limitation of the current study was the relatively small sample size. A larger study population may have enabled the exploration of potential significant differences between the investigated drugs. Therefore, we suggest that future studies should aim to recruit a larger sample size and consider evaluating the newer generation of biological drugs for the treatment of nail involvement in psoriatic arthritis.

**Authors’ contribution**
Conceptualization: Elham Rajaei.
Data curation: Amin Dadfar.
Formal analysis: Alireza Ghanbaran, Elham Rajaei, Amin Dadfar.
Funding acquisition: Elham Rajaei.
Investigation: Amin Dadfar, Elham Rajaei, Nader Paziar
Methodology: Alireza Ghanbaran, Elham Rajaei.
Project administration: Amin Dadfar.
Resources: Elham Rajaei, Nader Paziar, Alireza Ghanbaran.
Supervision: Elham Rajaei.
Validation: Amin Dadfar, Elham Rajaei.
Visualization: Elham Rajaei.
Writing—original draft: Amin Dadfar, Elham Rajaei.
Writing—review and editing: Amin Dadfar, Elham Rajaei, Alireza Ghanbaran.

**Conflicts of interest**
The authors declare that they have no competing financial or non-financial interests to report. The patients involved in this study prepared their own medications as part of their routine clinical treatment protocol. The authors of this research did not have any direct contact or engagement with the distributors of the drugs under investigation.

**Ethical issues**
This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The research protocol was reviewed and approved by the Clinical Studies Ethics Committee of Ahvaz University of Medical Sciences, Ahvaz, Iran (ethical code: IR.AJUMS.HGOLESTAN.REC.1400.155). Written informed consent was obtained from each patient prior to their participation in the study. Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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**References**


