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Research Article

Treatment Resistance to TNF-α Inhibitors in Patients with Psoriasis

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Background. Treatment resistance to biologic treatment at specific sites in the body is a challenging issue. However, there is insufficient evidence for factors affecting the resistance of these areas to biological therapies. *Methods*. In this study, patients with moderate-to-severetreatment-resistant psoriasis who were biologic naïve and referred to Razi hospital were included. The relationship between treatment resistance in different areas and demographic and clinical variables was investigated. *Results*. A total of 131 biologic-naïve patients with psoriasis treated with anti-TNF-α were included in this study. The most common resistant sites included the scalp, anterior lower legs, and elbows. Also, hand- and toe-nail involvements were considerable. BMI, gender, smoking, PASI score, the duration of the disease, the time distance between diagnosis and treatment, and treatment regiments were found to affect the incidence of resistance to treatment in multiple areas, while age, the incidence of recalcitrant disease and/or psoriatic arthritis, and the duration of current treatment did not have effects. *Conclusion*. The most common refractory sites were the scalp, anterior lower legs, and elbows. This study should be followed up with larger samples containing a variety of biological treatments in order to evaluate the results.

1. Introduction

Psoriasis is an autoimmune and chronic inflammatory papulosquamous disease that can affect various organs. The prevalence of this disease in the world is 1–3%. Psoriasis can occur at any age but is most common between the ages of 15–20 and 60–55 [1]. It manifests clinically as inflamed red plaques accompanied by silver scaling [2].

The etiology of this disease is explained by the interactions between genetic, environmental, and immunological factors [3]. Among the environmental factors, there are the usage of some drugs and skin trauma (known as the Koebner phenomenon) [4]. A great amount of effort has been put into finding an effective treatment for this condition. The most common treatment options include topical therapies, corticosteroids, vitamin D analogs, calcineurin inhibitors, and systemic therapies. There are several systemic treatments available, including cyclosporine, methotrexate, and biologics such as tumor necrosis factor (TNF) alpha inhibitors [5].

The inflammatory cascade in psoriasis begins with the activation of dendritic cells by skin surface antigens, which produce various cytokines, including interleukins (IL) 23, 12, and TNF-α. TNF-α is one of the most important proinflammatory cytokines which is made by T lymphocytes, macrophages, and keratinocytes [6]. The expression levels of this factor in the skin of patients with psoriasis are elevated. TNF-α also contributes to the production of other cytokines such as IL-1 and IL-6. Therefore, TNF-α inhibitors have been approved for the treatment of psoriasis for the past two decades, resulting in a promising therapeutic outcome [7].

Treatment resistance has been reported in psoriasis in specific areas of the body. However, based on the clinical observations, the resistance to treatment in these areas for biological therapies is much lower than for other common

treatments. On the other hand, there is insufficient evidence to prove the resistance of these areas to biological therapies. These areas include the palms and soles, nails, scalp, and skin folds. Furthermore, some studies have shown that nail and scalp lesions respond better to biological treatment compared to topical treatments [8]. Therefore, having the appropriate evidence about the resistance to treatment in these areas can help us to achieve the ultimate goal of treatment which improves the quality of life of patients by choosing the best method. In this study, we decided to investigate the areas of resistance to TNF-α inhibitors in patients with psoriasis who had never used biologic treatments.

2. Materials and Methods

The study was conducted as a noninterventional observation from January 2014 to December 2021 at a dermatology referral hospital in Tehran, Iran. We evaluated biologic-naïve patients with psoriasis vulgaris who were over 18 years old and had been treated with TNF-α inhibitors for at least 6 months and whose response to treatment had been satisfactory. From the patients' records, data regarding demographics, disease characteristics, underlying conditions, and treatment response was extracted. Patients' information was analyzed anonymously in a confidential and coded manner. In all cases, the personal information and collected information of the participants were preserved, and the consent of the participants was considered for the research. The principles of the Helsinki Declaration were followed. This study was approved by the Iran National Committee for Ethics in Biomedical Research (ethics code: IR.TUMS.MEDICINE.REC.1398.935).

Data were analyzed using the R open-source environment (R Foundation for Statistical Computing). Mean, standard deviation (SD), odds ratios (OR), and percentage indices were used to describe the data. The chi-square and Fisher's exact tests were used to analyze qualitative variables. An Independent T-test and Mann–Whitney U test were used to analyze quantitative variables. p values for post hoc tests were adjusted using Bonferroni's method. In all tests, a significance level of 0.05 was considered.

3. Results

In this survey, 131 biologic-naïve patients with psoriasis who had been treated with alpha TNF-α inhibitors were studied. Among them, 8 (6.1%) patients were treated with infliximab, 116 (88.5%) patients were treated with adalimumab, 7 (5.3%) were treated with etanercept, 77 (58.8%) patients were resistant to treatment, and 39 (29.8%) patients had psoriatic arthritis (Table 1). Table 1 provides information about the initial characteristics of the patients and their demographics. The most common resistant sites include the scalp (64.1%), anterior legs (49.6%), elbows (40.5%), anterior knees (29%), abdomen (24.4%), anterior thighs (19.1%), chest (16%), anterior forearms (15.3%), buttocks (11.5%), and face (8.4%). In addition, 39.7% of patients had hand-nail involvement, and 22.9% of patients had foot-nail involvement (Figure 1).

Due to the fact that the prevalence of resistance to treatment in some areas was very low, to investigate the relationship between demographic and clinical factors with the resistance to treatment in different areas of the body, the most common areas with resistance to treatment were selected. There was no significant relationship between patients' age and areas of resistance to TNF-α inhibitor therapies (Table 1 supplementary). Resistance to treatment in the anterior forearms (32 ± 1.66; 30.95 ± 3.39; $p = 0.037$) and anterior lower legs (31.91 ± 3; 30.32 ± 3.22; $p = 0.004$) was significantly associated with a higher BMI. Moreover, patients who had resistance to treatment in the anterior knees area (30.10 ± 3.32; 31.52 ± 3.08; $p = 0.026$) had a significantly lower BMI than patients without resistance to treatment in that area. For gender, women showed a significant increase in the prevalence of treatment resistance in anterior knees areas (OR: 2.32; $p = 0.049$), and a significant decrease in the prevalence of treatment resistance in hand-nails (OR: 0.41; $p = 0.024$) and foot-nails (OR: 0.39; $p = 0.024$) areas. Furthermore, smoking was associated with treatment resistance in the chest area (OR: 2.80; $p = 0.041$) and anterior legs (OR: 2.42; $p = 0.25$) (Table 1 Supplementary).

Regarding the disease characteristics, we found a significant relation between resistant lesions in the scalp (14.22 ± 5.99; 12.19 ± 2.98; $p = 0.049$) and hand nails (15.44 ± 6.45, 12.21 ± 3.68; $p = 0.001>$) and PASI scores. The duration of the disease was significantly shorter in patients with resistant lesions in the buttock (131.20 ± 90.08; 192.72 ± 105.29; $p = 0.025$) and the hand nail area (160.85 ± 96.93; 202.03 ± 107.80; $p = 0.025$) (Table 1 Supplementary).

Regarding the current treatment, the prevalence of resistance in the foot nails area was different between infliximab, adalimumab, and etanercept groups ($p = 0.004$). Following one-vs-rest post hoc tests, infliximab was found to be less effective in preventing resistance in the foot-nails area (OR: 15.84, adjusted $p = 0.007$). For previous treatments, the prevalence of resistance in foot nails ($p = 0.025$) and face ($p = 0.021$) areas was different between treatment groups (Table 1 Supplementary). Post hoc tests did not show any significant difference for any current treatment regiments (data not shown). Patients with treatment resistance in the anterior thighs area (22.48 ± 18.67; 38.44 ± 32.78; $p = 0.027$) and hand nails (29.35 ± 27.33; 39.37 ± 33.03; $p = 0.042$) had a significantly shorter time interval between diagnosis and treatment (Table 1 Supplementary).

4. Discussion

The present study investigated the areas resistant to treatment with TNF-α inhibitors and their relationship with demographic and clinical factors in biologic-naïve patients with psoriasis. We found a higher treatment resistance in the scalp, anterior lower legs, elbows, hand-nail, anterior knees, abdomen, foot-nail, anterior thighs, chest, anterior forearms, buttocks, and face.

Currently, eight biological therapies for moderate-to-severe or severe psoriasis have been approved (adalimumab, etanercept, nfliximab, ustekinumab, ixekizumab, secukinumab, brodalumab, and guselkumab). Treatment with TNF-α inhibitors (adalimumab, etanercept, and infliximab) has shown promising outcomes in the treatment of complicated psoriasis in resistance-treatment areas such as nail, scalp, and

Table 1: The initial and demographic characteristics of the patients.

Characteristic	Patients with psoriasis ($n = 131$)
Age (years; mean (SD))	45.06 (13.07)
BMI (kg/m^2; mean (SD))	31.11 (3.21)
Sex (n (%))	
Male	71 (54.2%)
Female	60 (45.8%)
Smoking (n (%))	42 (32.1%)
PASI (mean (SD))	13.49 (5.19)
Disease duration (months; mean (SD))	185.68 (105.20)
Diagnosis to treatment duration (months; mean (SD))	35.39 (31.77)
Previous treatments (n (%))	
Topical	22 (16.8%)
Whole-body phototherapy	7 (5.3%)
Cyclosporine	14 (10.7%)
MTX	79 (60.3%)
Retinoid	4 (3.1%)
Anti-TNF-α	5 (3.9%)
Current biologic treatments (n (%))	
Infliximab	8 (6.1%)
Adalimumab	116 (88.5%)
Etanercept	7 (5.3%)
Duration of the current treatment (months; mean (SD))	19.16 (15.11)
Recalcitrant disease (n (%))	77 (58.8%)
Psoriatic arthritis (n (%))	39 (29.8%)

SD: standard deviation; PASI: psoriasis area severity index; MTX: methotrexate.

palm involvement [9]. However, these results are limited because much of the data were extracted from retrospective studies, case reports, and subanalyzes of phase III trials that evaluate the efficacy and safety of TNF-α inhibitors for manifestations of psoriasis in treatment-resistant areas [9]. On the other hand, despite their excellent efficacy, patients with psoriasis who use biologic treatments often stop treatment or switch to another biologics since the efficacy of biologics usually declines with time. Despite recent publications about the long-term safety of biologic treatments for the treatment of psoriasis, little is known about which parts of the body are more resistant to them [10–12].

Egeberg et al. investigated the prevalence of treatment-resistant areas in psoriasis [13]. The most common resistant areas included the scalp, face, nails, heels, genitals, and palms. The higher prevalence of treatment resistance was associated with greater disease severity. Among all patients, 64.8%, 42.4%, and 21.9% of patients had more than 1, 2, and 3 treatment-resistant areas, respectively [13]. In a study by Callis Duffin et al. in the United States, all patients with psoriasis in the CORRONA registry from 2015 to 2018 who started biological therapy at the beginning of the registry were examined. Among them, 38.4% had psoriatic arthritis, 38.1% had scalp psoriasis, 16% had nail psoriasis, 10.9% had palmoplantar psoriasis, and 26.2% had a combination of these. They found that 65.8% of patients had lesions in resistant areas. Patients with involvement in treatment-resistant areas had higher pruritic scores than other patients. Patients with nail or palmoplantar involvement had higher pain and fatigue scores than patients who did not have involvement in these areas [14]. In another study, the most common resistant areas included the anterior tights, posterior tights, elbows, and scalp [15]. In our study, the most common treatment-resistant areas were the scalp, anterior lower legs, elbows, hand-nail, anterior knees, abdomen, foot-nail, anterior thighs, chest, anterior forearms, buttocks, and face (Figure 1).

In a study, it has been shown that an increase in BMI was associated with a higher incidence of psoriasis, but they did not find any association between BMI and areas of resistance to treatment [16]. Similarly, smoking directly caused more severe psoriasis [17]. Nicotine in cigarettes may induce resistance to treatment by binding to its receptors and facilitating the binding of keratinocytes and upward migration in the epidermis [18].

Consistent with the present study, prior studies have shown that higher disease severity is associated with the development of resistance in different areas, which is probably due to less responsiveness to treatment in cases of higher disease severity [13]. Nevertheless, more studies are needed to directly examine the context and the cause of the relationship between these factors and the development of resistance in different areas.

Data regarding the reasons for difficult-to-treat locations in psoriasis are not well understood. An explanation could be provided by the role of tissue-resident memory (TRM) T cells in psoriasis pathogenesis. TRM-T cells are believed to play an important role in the development and persistence of treatment-resistant forms of psoriasis by producing and releasing a wide range of proinflammatory cytokines (such as TNF-alpha and IL-17) which contribute to the inflammatory process and psoriasis symptoms. The persistence of TRM-T cells in affected skin areas may be one reason why psoriasis can become treatment-resistant. In addition, TRM-T cells are

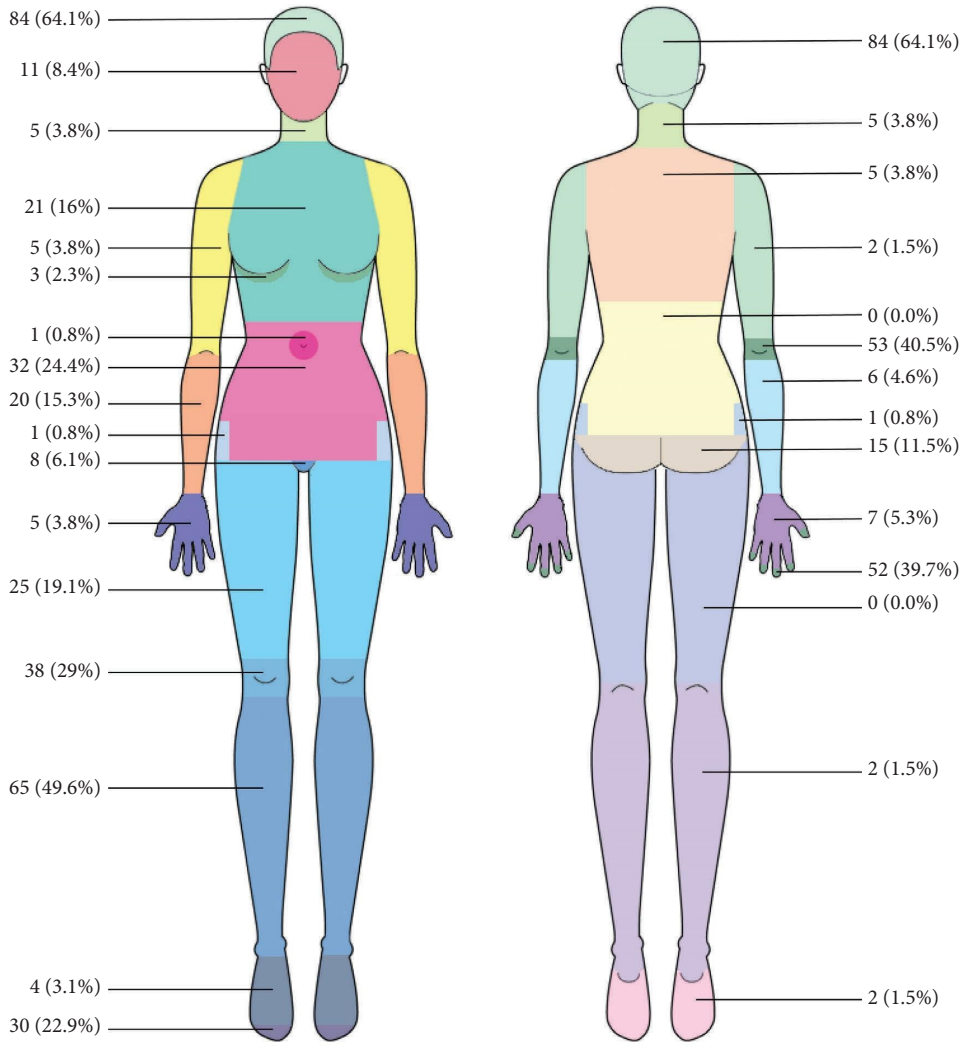

Figure 1: The frequency of resistance to treatment in each area.

less susceptible to many treatments due to their enhanced responsiveness and ability to survive cell death. As a result of this resistance, inflammation and the progression of the disease can continue despite treatment. TRM-T cells can be reactivated by various triggers, such as skin injuries, infections, or stress, resulting in psoriasis flare-ups. Ultimately, it appears that resident TRM-T cells can be one of the most important factors contributing to resistance to the treatment of psoriasis, if not the leading cause. Thus, focusing on suppressing or apoptosis of TRM-T cells could be a promising approach to controlling psoriasis, particularly in difficult-to-treat cases [19, 20].

There are still many questions regarding the cause and mechanism of biological resistance at specific sites in the body. Through this study, we have attempted to gain a deeper understanding of the clinical characteristics of this phenomenon. Considering the fact that minor trauma contributes to the beginning step for psoriasis lesion development, the majority of treatment-resistant sites are located in locations that are susceptible to trauma, such as the extremities, scalp, and nails.

As the history of previous biologic exposure and resistance has a significant impact on the efficacy of other biologic drugs, we have limited our study to patients who are biologic-naïve. Furthermore, only experienced PASI assessors working in psoriasis clinics at universities participated in the study. There are also limitations to the study. An important limitation is that we have focused exclusively on anti-TNF-α inhibitors, and other biologic treatments were not included. Thus, larger studies with different biologic therapies are required to characterize in greater detail the localizations of psoriasis prior to treatment. In addition, we did not evaluate the impact of biologic-resistant areas on the quality of life of patients with psoriasis, which requires further investigation.

5. Conclusions

The present study investigated areas resistant to TNF-α inhibitors in patients with psoriasis. Furthermore, we investigated the relationship between treatment resistance in different areas and demographic and clinical variables. The

most common resistant sites were the scalp, anterior lower legs, elbows, hand-nail, anterior knees, abdomen, foot-nail, anterior thighs, chest, anterior forearms, buttocks, and face. Also, multiple factors were found to be related to the incidence of resistance to treatment in multiple areas. In order to fully investigate the results of this study, we recommend larger sample sizes and more diverse groups of biologic treatments that should be conducted in future studies.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

Amirmansoor Gholami and Ahmad Vafaeian are the co-first authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Amirmansoor Gholami and Ahmad Vafaeian contributed equally to the work.

Supplementary Materials

Supplementary material includes the table of comparative analyses of patients' characteristics and the localization of resistance at the most prevalent sites. (*Supplementary Materials*)

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