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Efficacy and Safety of Adalimumab 40 mg Weekly Dosingin Patients with Resistant Psoriasis

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Authors' contributions

This work was carried out in collaboration between both authors. Author MT designed the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript, and managed the analyses of the study. Author SD managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Background: The recently updated dosing recommendation for adalimumab for psoriasis states that patients with inadequate response to adalimumab every other week (EOW) after 16 weeks may benefit from an increase in dosing frequency to 40 mg every week (EW).
Objectives: This study aims to investigatethe efficacy and safety experience of dose escalation of adalimumab to 40 mg weekly dosing patients with psoriasis with suboptimal response to 40 mg EOW dosing.
Methods: In this report 22 moderate-to-severe psoriasis patients treated with 40 mg adalimumab EW were evaluated retrospectively. Primary endpoints were safety and efficacy of treatment defined as statistically significant improvement of PASI and PGA in the 24 week of therapy.
Results: A total of 22 patients enrolled. Patients were under adalimumab 40 mg EOW therapy for a 16 weeks-1 year. We observed a rapid and significiant reduction of PASI and PGA scores in W4. By week 24, 95, 45% (n=21) of patients achieved ≥PASI 75, 72, 72% (n=16) of patients achieved ≥PASI 90 and 40, 9% of patients achieved PASI 100 response. The percentage of patients patients who achieved a PGA 'Clear' or 'Almost Clear' was 77, 27% (n=17) at W24. Dose escalation of adalimumab provided the achievement and long-term maintenance of clinical

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improvement in these patients. No side effects were observed during 40 mg EW adalimumab treatment.
Conclusions: Dose escalation could be a good approach for increasing efficacy in a subgroup of patients with an insufficient response to adalimumab, reducing symptoms of psoriasis.

Keywords: Psoriasi; adalimumab; treatment; dose escalation.

1. INTRODUCTION

Psoriasis is a chronic inflammatory disease of skin affecting 1-3% of the population. [1] Psoriasis is associated with considerable comorbidities like metabolic syndrome, hypertension, diabetes mellitus, inflammatory bowel disease and psoriatic arthritis and reduced quality of life [2,3]. Therapy for psoriasis varies by disease severity, with moderate-to-severe disease treated with phototherapy, traditional systemic treatments (oral retinoids, cyclosporine, methotrexate) and biologic agents. Traditional systemic treatments are efficacious but limited over time by dose-dependent adverse events or may be contraindicated in those with comorbidities [4,5]. Improved understanding of the immunopathogenesis of psoriasis has led to the development of biologic agents targeting the immune cells and cytokines [4,5]. In recent years, use of biologic agents for patients with moderate-to-severe psoriasis has increased for their safety, efficacy and no cumulative organ toxicity [6].

Tumor necrosis factor (TNF) alpha is a key pro-inflammatory cytokine with a central role in pathogenic mechanisms linkingpsoriasis and anti-TNF therapy is one option recommended for the moderate-to-severe psoriasis in whom traditional therapies fail to produce an adequate response or are not-tolerated [6]. Adalimumab is a fully human monoclonal antibody specific for TNF alpha that has been approved for the treatment of moderate-to-sever plaque psoriasis at an initial dose of 80 mg followed by 40 mg administered subcutaneously every other week (EOW) [7]. Response to biologic therapies remain subjective and patients can develope resistance to standart therapy dose. Dose escalation (reducing intervals or increasing dose) represent modification strategies that can be used in real life [8]. Before switching to another systemic agent, it is recommended to first use these strategies [8]. Dosing recommendation was recently updated to state that patients with inadequate response to adalimumab EOW after 16 weeks may benefit from an increase in dosing frequency to 40 mg every week (EW) on new study findings [9].

This manuscript presents the efficacy and safety experience of dose escalation of adalimumab to 40 mg weekly dosing patients with psoriasis with suboptimal response to 40 mg EOW dosing.

2. MATERIALS AND METHODS

One hundredninety-eight patients with moderate-to-severe psoriasis were under adalimumab therapy in our dermatology clinic, Izmir Bozyaka Training and Research Hospital. After loading dose we observed loss of clinical efficacy of adalimumab 40 mg EOW in 22 patients, their PASI scores started to increase and we optimized therapy by increasing the dosing of adalimumab to 40 mg EW. In this report 22 moderate-to-severe psoriasis patients treated with 40 mg adalimumab EW were evaluated retrospectively. The demographic features and clinical data of the patients (age, gender, previous treatments) were evaluated. All patients met the following criteria; (1) affected by chroinc plaque psoriasis (2) showed inadequate response to adalimumab EOW after 16 weeks (PASI≤50).

2.1 The Primary Efficacy End Points of this Study were the Followings

(1) The efficacy of CZP as defined by the significant improvement of Psoriasis Area and Severity Index (PASI) and a physician's global assessment (PGA) of psoriasis severity. (Seven point scale ranges from 'Clear' to 'Severe') (2) Safety of 40 mg adalimumab EW as defined by the occurence of adverse events during the study.

The findings of dermatologic pyhical examination of patients and the values of PASI and PGA scores of recorded at baseline (W0), week 4 (W4), week 12 (W12) and week 24 (W24) of adalimumab 40 mg EW treatment were evaluated. Laboratory test results recorded (including complete blood ccount test, liver and renal function tests, urinalysis, erythrocyte. sedimentation rate (ESR, mm/h) and C-reactive protein (CRP, mg/dl) were evaluated.

2.2 Statistical Methods

Baseline demographics, duration of treatment were summarized using descriptive statistics). PASI results for the dose-escalation population included data relative to the time the patient received the first dose escalation. Week numbers are presented relative to the first dose escalation and data are presented only to week 24 when evaluating initial dose escalation. Statistical analysis was performed with IBM SPSS 20.0 software. All values are showed as mean ± standard error of the mean (SEM) unless otherwise stated.

3. RESULTS

The ages of 22 patients receiving adalimumab 40 mg weekly for moderate-to-severe psoriasis were between 23-62 (mean: 43, 62±2, 4) and 13 of the patients were male The disease duration ranged from 7 to 33 years (mean 18±3, 2 years). Eight patients were naive to biologic treatment. (Table 1) Fourteen have previously been treated with Other biologic Treatments with no response; 9 patients have been treated with an anti-TNF therapy (4 infliximab/ 5 etanercept); 5 patients have been treated with interleukin (IL) blockers (3 secukinumab, 2 ustekinumab). The patients were under adalimumab 40 mg EOW therapy for a 16 weeks-1 year (mean 6, 4 ± 2, 1 months).The mean PASI score of patients were 17, 8±1, 22 at baseline of the study and decreased to 4, 3±0, 74 at W4. All patients achieved PASI 75 response at W4. By week 24, 21 patients (95, 45%) achieved ≥PASI 75, 16 patients (72,72%) achieved ≥PASI 90 and 9 patients (40, 9%) achieved PASI 100 response. (Fig. 1)

At baseline the majority of patients (20/22- 90, 90%) had at least moderate psoriasis by PGA. The percentage of patients who achieved a PGA 'Clear' or 'Almost Clear' was 77, 27% (17/22) at W24.

No laboratory abnormolities and clinical side effects were observed during 40 mg EW adalimumab treatment.

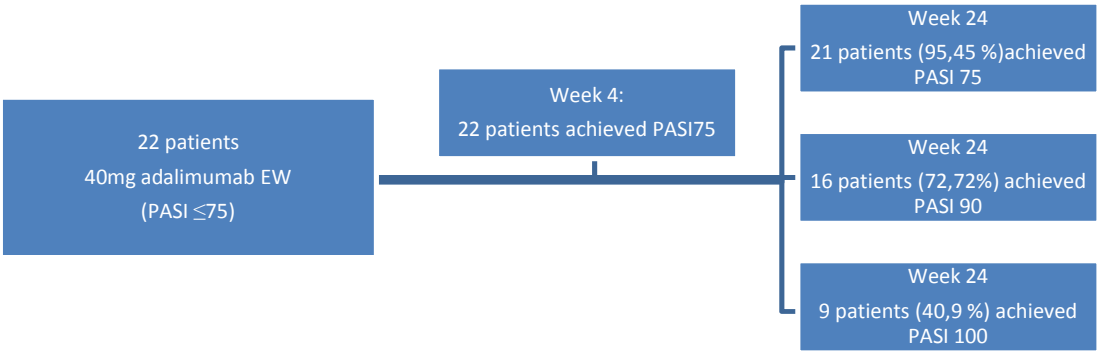

Fig. 1. Efficacy of 40mg adalimumabadministeredweeklyevaluatedby PASI responses

Table 1. Characteristics of patientswithpsoriasistreatedwith 40 mg weeklyadalimumabtherapy

Number of patients	22
Female, n (%)	9 (40, 90)
Male, n (%)	13 (59, 09)
Age, years (mean ± SD)	23-62 (mean: 43, 62 ± 2, 4)
Duration of disease,years (mean± SD)	7-33 years (mean 18 ± 3, 2 years)
Duration of 40mg adalimumabtherapy EOW, months (mean ± SD)	6, 4 ± 2,1
Biologicnaivepatients (n)	8
Biologic-exposedpatients (n)	14

SD: Standard deviation

4. DISCUSSION

Compared with the abundance of information available regarding the efficacy and safety of biologic therapies derived from phase III clinical studies, relatively little published information is available to help physician's decision-making about the management of patients who are experienced with a therapy but are having loss of clinical efficacy [6]. Psoriasis treatment guidelines recommends first dose escalation in a patient who is suboptimally responsive to a biologic agent before switching to another systemic agent [10,11]. Adalimumab is a biologic agent that leds itself enough todose escalation by more than other biological dose thanks to itssimilarity from human IgG1 and to less immunogenic action than other biologic drugs; this is the reason of his prolonged durationof action [12].

Leonardi et al. [12] reported in an open-label extension study of patients with psoriasis who had an inadequate response to adalimumab 40 mg EOW, escalation to adalimumab 40 mg EW was beneficial in achievingor regaining treatment response. In that study, 27.8% of patients had their dose escalated from adalimumab 40 mg EOW to 40 mg EW after having <50% improvement in PASI 50score at or after 24 weeks of treatment. After dose escalation, 38.1% of the patients achieved≥75% improvement in PASI (PASI 75) after 24 weeks, suggesting that dose escalation of adalimumab to EW dosing can benefitsome patients with an inadequate response to EOW dosing. After increasing the dose of adalimumab from 40 mg EOW to 40 mg EW a we observed a rapid and significiant reduction of PASI and PGA scores in W4. Dose escalation of adalimumab permitted the achievement and long-term maintenance of clinical improvement in these patients.

Gniadecki et al. [9] studied longterm efficacy of adalimumab with flexibility to escalate anddde-escalate between EW and EOW dosing regimens. They emphasized that optimizing therapy by temporarily increasing the dosing frequency of adalimumab to EW in patients who had an inadequate response to adalimumab 40 mg EOW permitted the achievement and long-term maintenance of clinical improvement. They reported that after escalation of adalimumab dosing to EW, approximately one quarter of patients were able to successfully have their dose de-escalated and remain on EOW dosing for nearly 1 year without the need for dose re-escalation[9].

The safety results for 40 mg weekly dosing and 40 mg eow dosing reported in the phase II dose-ranging study [12] of adalimumab for psoriasis, as well as results from analogous dose-ranging studies of adalimumab for rheumatoid arthritis and Crohn's disease [13-15]. Weekly adalimumab dosing was well tolerated and no side effects were observed in patients during 40 mg weekly adalimumab treatment in our study.

5. CONCLUSION

In conclusion, dose escalation could be a good approach for increasing efficacy in a subgroup of patients with an insufficient response to adalimumab, reducing symptoms of psoriasis.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

This is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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