ORIGINAL ARTICLE

ORIGINAL CLINICAL EXPERIENCE AND APPROACH TO TREATMENT STUDY WITH INTERLEUKINE 12/23 INHIBITOR IN MODERATE-TO-SEVERE PSORIASIS PATIENTS

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Abstract

In recent years, there has been an increasing interest in developing new biologic treatments for psoriasis. Ustekinumab, an interleukin (IL) IL12/IL23 inhibitor, has demonstrated real efficacy in treatment of psoriasis and psoriatic arthritis. We aimed to describe our centre's experience with this therapy. We included 15 patients (mean age 50.6 years and 2:1 male/female ratio) with moderate-to-severe psoriasis, followed for 12 months. Over the course of the study, the patients received ustekinumab as per usual protocol. Psoriasis area and severity index (PASI) and dermatological life quality index (DLQI) scores were measured at 1, 3, 6, 9 and 12 months, PASI75 being the primary endpoint. A significant improvement in both PASI and DLQI scores was seen in the first 16 weeks, with a *plateau* up until week 52. All patients achieved PASI75 and 93.3% PASI90 by month 12. Our experience with ustekinumab in the treatment of moderate-to-severe psoriasis showed excellent results, with all patients reaching the primary endpoint of PASI75 by month 12. Further studies are needed to determine long term efficacy and safety.

Rezumat

Recent, cercetările au condus la descoperirea unor noi terapii biologice în psoriazis. Ustekinumab, inhibitor de interleukină (IL) IL12/IL23, s-a dovedit inovator și eficient în psoriazis și artrita psoriazică. Scopul studiului de față a fost de a descrie experiența în privința utilizării acestei terapii. 15 pacienți (vârsta medie 50,6 ani, raport bărbați/femei de 2/1) cu psoriazis vulgar, forma moderat-severă, au fost selectați și urmăriți timp de 12 luni, după administrare de ustekinumab conform protocolului. Scorurile PASI (*psoriasis area and severity index*) și DLQI (*dermatological life quality index*) au fost evaluate la 1, 3, 6 respectiv 12 luni, PASI 75 fiind *endpointul* primar. O îmbunătățire semnificativă s-a observat în săptămâna 16, urmată de o fază de platou până în săptămâna 52. La sfârșitul studiului, toți pacienții au atins PASI75, iar 93,3% - PASI90. Experiența noastră cu ustekinumab în terapia psoriazisului vulgar moderat-sever a arătat rezultate excelente, toți pacienții atingând *endpointul* primar de PASI75 până în luna 12. Studii ulterioare sunt necesare pentru a determina eficiența și siguranța administrării pe termen lung.

Keywords: psoriasis, IL12/23 inhibitor, biological therapy

Introduction

Psoriasis is a chronic immune-mediated inflammatory disease with great impact on the patient's quality of life affecting the skin, but also the joints together with its comorbidities.

There is a large amount of information regarding the functional and immunological significance of the cytokine repertoire involved in psoriasis, including IL17, IL21, IL22, or IL4 [6]. Patients with moderate-to-severe psoriasis unresponsive to local or conventional therapy may now benefit from the treatment with new biological agents like anti-tumour necrosis factor alpha (anti-TN alpha), anti IL12/IL23 and others [1, 12].

Ustekinumab is a monoclonal antibody targeting the p40 subunit common to IL12 and IL23, thus preventing the interactions of those two cytokines with their receptors and blocking Th1 and Th17 inflammatory pathways that lead to psoriasis [2]. The aim of this study was to assess the effect of ustenkinumab therapy of Romanian psoriasis patients from 2 centres, Bucharest and Iasi, Romania.

Materials and Methods

This was a prospective, observational study performed in order to evaluate the efficacy of ustekinumab, conducted in Colentina Clinical Hospital from Bucharest and "Sf. Spiridon" Hospital Iasi. Eligible

patients had a clinical diagnosis of moderate-to-severe chronic psoriasis, defined by a Psoriasis Area and Severity Index (PASI) and Dermatological Life Quality Index (DLQI) score of 10. All considered patients are qualified as candidates for systemic therapy, using usual protocols for all biologic therapy in moderate to severe psoriasis [7]. Both naive and previously treated with other regimens patients were included.

Ustekinumab was provided by Johnson & Johnson© in a "Named Patient Programme" used to give access to a medicine on an individual patient basis, who in the physicians clinical judgement has an un-met medical need and for whom there is no alternative treatment currently available. All the patients included in this programme for a 12 months therapy had signed an inform consent before enrolment. The clinical study was approved by the Ethical Committees of the two medical institutions.

Dosing was as follows: 45 mg x 5 = 225 mg ustekinumab in 12 months (for patients under 100 kg) b.w. and 90 mg x 5 = 450 mg/12 months (for patients over 100 kg) b.w. The treatment regimen comprised doses at week 0, week 4 and then every 12 weeks.

Gender, age, the previous biological treatment and the presence of arthritis were noted, at the first visit. Each patient was further evaluated at 1, 3, 6, 9 and 12 months, PASI and DLQI were calculated. The main outcome is the achievement of PASI75. Other endpoints include PASI50, PASI90 and reduction in DLQI.

Continuous variables were presented as mean (± standard deviation). Proportions were compared with the Fisher exact test, baseline continuous variable distributions using the Student t-Test or the Mann-Whitney U test, as required. Overall changes in PASI and DLQI scores over time were evaluated with the repeated-measures ANOVA test, using the Bonferroni adjustment for multiple testing in post-hoc between-groups testing. Time-to-event analysis was performed using the Kaplan Meier method. Statistical analyses were done with STATA/IC 11.2 (StataCorp LP, College Station, TX).

Results and Discussion

A total of 15 patients were included, with a mean age of 50.6 (12.8) years and a male/female ratio of 2:1. Five patients had previous therapy as follows: 2 had adalimumab, 1 had etanercept, 1 had infliximab in a single therapy and the last had infliximab and adalimumab. A third (5/15) of patients had arthritis. Patients with arthritis were significantly older than those without arthritis (mean 59.6 *vs.* 46.1 years, p = 0.02, one side test). No differences in age were seen by gender or previous treatment.

There was a significant improvement of both PASI (Figure 1) and DLQI (Figure 2) scores over the 12 months study period. In terms of the PASI score, there were significant decreases from week 1 to week 4 (mean of 24.1 *vs.* 9, $p < 0.001$) and also from week 4 to week 16 (mean of 9 *vs.* mean of 1.8, $p < 0.001$), with only minor differences in the following intervals.

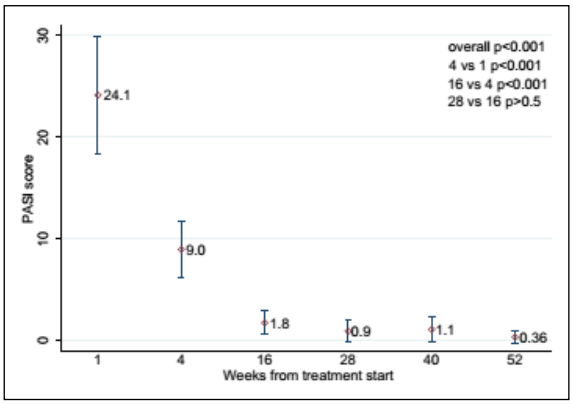

Figure 1.
PASI progression over 52 weeks

The same pattern followed the DLQI scores, with significant decreases from week 1 to week 4 (mean of 18.7 *vs.* 9.1, $p < 0.001$) and also from week 4 to week 16 (mean of 9.1 *vs.* mean of 1.5, $p < 0.001$), and minor decreases after week 16. Both scores exhibited an abrupt decrease by week 16 and maintained a plateau up to week 52.

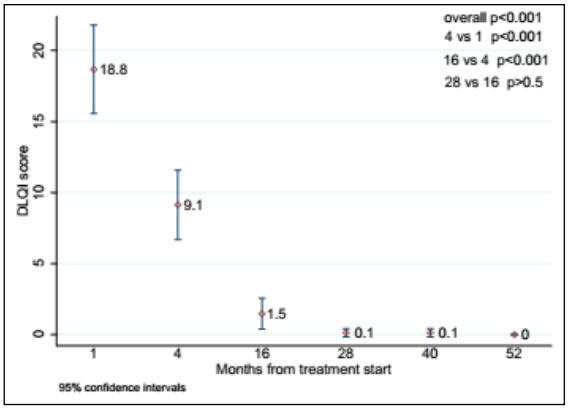

Figure 2.
DLQI progression over 52 weeks

The proportion of patients achieving PASI75 and PASI90 at measured time intervals is shown in Figure 3. All patients achieved PASI75 by 12 months, with one patient failing to reach PASI90 at 12 months. This single patient had the lowest baseline PASI score (13) but failed to reach the

decrease endpoint. By month 3 the majority of patients had achieved PASI90.

The mean time to PASI75 was 3.2 (2.6) months, while mean time to PASI90 was 4.3 (2.7) months. No differences by gender, previous treatment or arthritis were seen, although the group was not sufficiently large to provide enough statistical power for proper subgroup analysis. There were no observed adverse reactions in our group, no patient discontinued or was lost to follow-up.

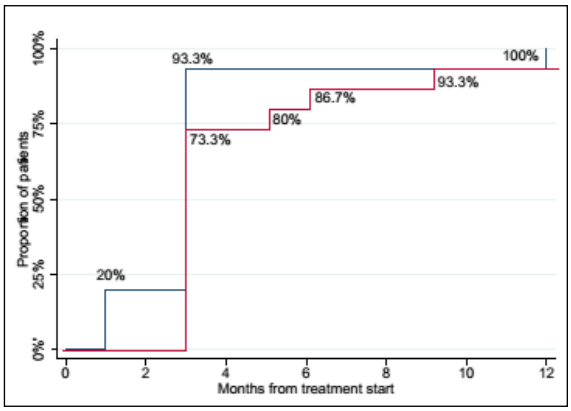

Figure 3.
Progression to PASI75 and PASI90 endpoints

The clinical efficacy of ustekinumab was observed within the first month of treatment, with a plateau being observed after week 16. There were no significant differences in terms of treatment response by gender, presence of psoriatic arthritis or status of previous biological therapy. Ustekinumab was well tolerated and there were no drug related adverse reactions in our study group, similar to previously reported results [11].

Between 1st and 3rd month of follow up, consistent PASI75 and 90 responses were observed in ustekinumab-treated patients and by month 3, the majority of subjects achieved PASI75 response (93.3%) and PASI90 response (73.3%). Only one patient failed to achieve PASI90 during the study period.

The impact of this treatment over the patients was evaluated through DLQI. DLQI had an improvement pattern similar to the PASI score, with a steep decrease by week 16 and a plateau up to week 52. Patient compliance with the treatment regimen was 100%.

The results of this study suggest that ustekinumab is generally safe and efficacious with a rapid response rate in our centre's experience. A rapid clinical response was observed (as early as week 4) with improvements in both PASI and DLQI scores up to a plateau after week 16. Efficacy was well maintained in this study, in which patients continuously received the same dose of ustekinumab for one full year without interruption or dose adjustment and these data are generally comparable with those reported in the literature [9].

We can highlight the finding that there were no differences regarding obesity and PASI behaviour [8].

Limitations. This is a small multicentre study with a small sample size, so it did not permit any meaningful subgroup analyses [5]. The relatively short follow-up might not permit the identification of adverse reactions or immunogenicity of the drug.

Conclusions

The data presented in this study adds to the augmentation of the published work regarding the use of biologics in patients and support the use of ustekinumab as a new, highly effective option in patients with moderate-to-severe psoriasis. The benefit-risk profile in the studied group was favourable, consistent with the global studies of ustekinumab [3, 4, 10].

Overall, our study suggests that ustekinumab can be an effective alternative therapy for moderate to severe psoriasis, but further additional studies are needed to evaluate long-term administration and the safety profile.

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