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Does the response to bimekizumab vary according to previous therapy with methotrexate *versus* cyclosporine?

Ilaria Salvi,[1] Alexandra M. G. Brunasso,[2] Franco Castelli,[3] Andrea Michelerio,[4,5] Paolo Pella,[6] Marco Rubatto,[7] Paolo Dapavo,[3] Emanuele Cozzani,[1] Martina Burlando[1]

[1]Section of Dermatology, Department of Health Sciences, University of Genoa, IRCCS Ospedale Policlinico San Martino, Genoa; [2]Department of Internal Medicine, Villa Scassi Hospital, ASL3, Genoa; [3]Section of Dermatology, Koelliker Hospital, Turin; [4]Department of Dermatology, Cardinal Massaia Hospital, Asti; [5]Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia; [6]Dermatology, Ospedale degli Infermi, Biella; [7]Candiolo Cancer Institute FPO-IRCCS, Candiolo (TO), Italy

Correspondence: Martina Burlando, Section of Dermatology, Department of Health Sciences, University of Genoa, IRCCS Ospedale Policlinico San Martino, via A. Pastore 10, 16132 Genova, Italy. E-mail: martina.burlando@uinge.it

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Ethics approval and consent to participate: this study was conducted in accordance with the Declaration of Helsinki; written informed consent was obtained for patients' information to be published in this article.

Availability of data and materials: the data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest: the authors have no conflict of interest to declare.

Abstract

According to the Italian Medicines Agency (AIFA) guidelines, patients with moderate-to-severe psoriasis can access biological therapies in case of treatment failure or contraindication to at least one conventional systemic treatment. However, no studies have been conducted to investigate the potential influence of previous conventional systemic treatments on the efficacy of subsequently prescribed biologics. The purpose of this study was to evaluate whether patients treated with bimekizumab, a monoclonal anti-interleukin (IL)-17A/F drug, achieve Psoriasis Area and Severity Index (PASI) 90 at different times based on prior use of cyclosporine or methotrexate. Fifty-four patients were enrolled in this study; 29 had previously been treated with methotrexate and 25 with cyclosporine. There was a statistically significant difference in efficacy (measured by mean PASI score) at week 4 ($p<0.01$), with patients treated with methotrexate responding faster to bimekizumab. Females previously on treatment with cyclosporine responded better and faster, followed by females on methotrexate and then men on methotrexate. Men on cyclosporine showed a later response to bimekizumab. Our study confirmed that bimekizumab is a fast and effective biologic treatment for psoriasis. Patients previously treated with methotrexate responded faster to bimekizumab than those formerly treated with cyclosporine.

Introduction

According to the Italian Medicines Agency (AIFA) guidelines, patients with moderate-to-severe psoriasis can access biological therapies in case of treatment failure or contraindication to at least one conventional systemic treatment.[1]

The most commonly used traditional drugs are cyclosporine and methotrexate. Patients treated with these drugs have been reported to achieve a 75% or more significant reduction in Psoriasis Area and Severity Index score from baseline (PASI 75) in 36-41% and 50-80% of cases at 16 or 8 weeks, respectively.[2] However, they may have side effects that make them unsuitable for long-term use.[2]

Cyclosporine is used at a dosage between 3 and 5 mg/kg/day. The higher the dosage, the faster the action, but the more frequent the side effects. Moreover, when the treatment is discontinued, the patient may experience a relapse.

On the other hand, methotrexate is used at dosages between 7.5 and 25 mg per week. It has a slower action than cyclosporine, especially at low dosages (10-15 mg/week).[3-5]

Currently, no studies are exploring the potential influence of previous conventional systemic treatments on the efficacy of subsequently prescribed biologics.

This study aims to evaluate whether patients treated with bimekizumab,[6] a monoclonal anti-interleukin (IL)-17A/F drug, achieve PASI 90 at different times based on prior use of cyclosporine or methotrexate.

Materials and Methods

Patients over 18 years old who had moderate-to-severe psoriasis for at least 6 months and had been on methotrexate or cyclosporine therapy for a minimum of 6 months were enrolled in the study. Only those patients who had discontinued such treatments within 4 weeks due to inefficacy or side effects were selected. Informed consent was obtained from all enrolled patients.

All patients were treated with bimekizumab 320 mg every 4 weeks for 16 weeks and every 8 weeks thereafter. The patients' demographic characteristics were collected. The PASI and Dermatology Life Quality Index (DLQI) scores were recorded at week 0 (T0), after week 4 (T1), and at week 24 (T2), as well as any adverse events reported.

Results

Fifty-four patients (33 male and 21 female) were enrolled in this study. The mean age was 65±15 years. Of these, 29 had previously been treated with methotrexate and 25 with cyclosporine (as shown in Table 1). The disease duration was 17±8 years in the methotrexate group and 18±5 years in the cyclosporine group. The body mass index (BMI) was 24.9±4.4 for the methotrexate group (22.3±3.3 for females and 26.1±4.6 for males) and 24.8±5.4 for the cyclosporine group (21.4±5.4 for females and 26.3±5.5 for males).

For patients treated with methotrexate, the average treatment time was 96±52 weeks. The initial prescribed dosage was 10 mg/week in patients weighing 80 kg or lower and 15 mg/week in patients weighing more than 80 kg. In case of inefficacy after 3 months, the dosage was increased by 2.5 mg/week every month up to a maximum dosage of 25 mg/week. Methotrexate was discontinued in 10/29 (34.5%) patients because of inefficacy and in 19/29 (65.5%) patients because of side effects, specifically nausea in 8/19 patients and persistently increased liver enzymes in 11/19 patients.

For patients treated with cyclosporine, the average treatment time was 42±29 weeks. The prescribed dosage was 3.5 mg/kg/day in all patients. Cyclosporine was discontinued in 20/25 (80%) patients because of side effects (increased creatinine, hypertension, hypertrichosis, and nausea) and in 5/25 (20%) patients because of inefficacy.

As per our common practice, no women of childbearing age were treated with methotrexate, and cyclosporine was the treatment of choice in this category of patients. The patients were advised to avoid pregnancy while on treatment but were allowed to choose the form of contraception.

At baseline (T0), the mean PASI score (mPASI) for those previously treated with methotrexate was 18.1±7.5, and the mean DLQI (mDLQI) was 15.4±7.6. For those on cyclosporine, the mPASI and mDLQI were 17.1±6.9 and 14.4±6.6, respectively (Figures 1-3).

After four weeks (T1), the PASI score and the DLQI decreased, reaching the scores of 2.9±3.0 and 3.4±7.7 in the methotrexate group, and 5.0±3.8 and 3.8±3.0 in the cyclosporine group (Figures 1-3).

After 24 weeks (T2), the mPASI was 1.3±2.0 and the mDLQI was 1.7±2.4 in the methotrexate group, while in the cyclosporine group, the mPASI was 1.6±1.9 and the mDLQI was 2.2±2.1 (Figure 1-3).

The results were also evaluated according to gender. At T0, the mPASI score for females was 16.1±8.2 and the mDLQI was 15.6±4.9; for males, it was 19.2±7.1 and 15.3±8.9 in the methotrexate group. In the cyclosporine group, the mPASI score for females was 16.6±5.2 and the mDLQI was 16.3±4.5; for males, it was 17.5±8.1 and 12.9±7.7.

At T1, the mPASI and mDLQI were 2.0±3.6 and 4.3±7.1 for females and 3.4±2.6 and 2.9±8.0 for males in the methotrexate group. In the cyclosporine group, the mPASI and mDLQI were 4.0±3.4 and 4.5±2.8 for females and 5.8±4.0 and 3.3±3.2 for males.

At T2, the mPASI and mDLQI were 1.3±1.3 and 2.4±2.5 for females and 1.3±2.3 and 1.3±2.4 for males in the methotrexate group. In the cyclosporine group, the mPASI and mDLQI were 0.6±1.0 and 3.2±2.0 for females and 2.3±2.2 and 1.5±1.8 for males.

None of the enrolled patients experienced side effects related to the treatment with bimekizumab.

Discussion

Many options are available to treat psoriasis today, including the latest anti-IL-17 treatments, which have proved to be very fast and effective.[7] Bimekizumab is the newest addition to the market, and 68% of the patients treated with it have been reported to achieve PASI 90 after only 4 weeks, with this rate increasing over time.[8] Clinical trials have shown that its rapidity and efficacy are not affected by previous biologic therapy.

However, it is currently unknown whether previous systemic therapy could affect the rapidity and efficacy of a biologic drug. Our study aimed to investigate any differences in response between patients who had discontinued methotrexate or cyclosporine immediately before starting treatment with bimekizumab.

Our study showed no difference between the two groups regarding efficacy at week 24. However, there was a statistically significant difference in efficacy at week 4 ($p<0.01$), with patients treated with methotrexate responding faster to bimekizumab. This may be explained by the fact that the

interruption of cyclosporine is often followed by a disease relapse, which could reduce the rapidity of the following therapy.[4]

Interestingly, when looking at the results from a gender perspective, females on cyclosporine responded better and faster, followed by females on methotrexate and then men on methotrexate. Men on cyclosporine showed a later response. These results differ from what was previously stated but may be explained by the body weight of the patients involved in the study, as females typically have a lower body weight, which can interfere with the speed and efficacy of a drug.[9]

Concerning the impact of psoriasis on the quality of life, which was evaluated with the validated DLQI questionnaire, we found that, on average, female patients presented a higher impact on the quality of life despite having a lower mean PASI, although without statistical significance.

This finding confirms the results of other studies, which have shown women to be more likely than men to report impairment of psoriasis-related quality of life.[10] This has been explained by the impact of psoriasis on body appearance and by the greater importance attributed to body image by female patients compared to male patients.[10]

Nonetheless, our study found that DLQI scores significantly decreased both at 4 and 16 weeks after treatment initiation. We did not find any significant differences in DLQI scores between those previously treated with methotrexate and those previously treated with cyclosporine.

Our study had some limitations, such as the small number of patients enrolled and the focus on only one biologic. Nonetheless, this is the first study to investigate the influence of a previous traditional systemic therapy on the rapidity and efficacy of a biologic drug.

Conclusions and Relevance

Findings from our study suggest that previous systemic treatments could affect the rapidity and efficacy of a biologic drug. In particular, although bimekizumab has shown good efficacy and rapidity in all patients, those previously treated with methotrexate responded faster than those formerly treated with cyclosporine. This result could be interpreted as a consequence of the relapse of psoriasis, which is expected after the interruption of cyclosporine. This information may offer some guidance to dermatologists in the choice of conventional systemic treatments in patients with moderate-to-severe psoriasis. Moreover, in light of these results, patients could be better informed concerning the expected rapidity of action of the treatment with bimekizumab.

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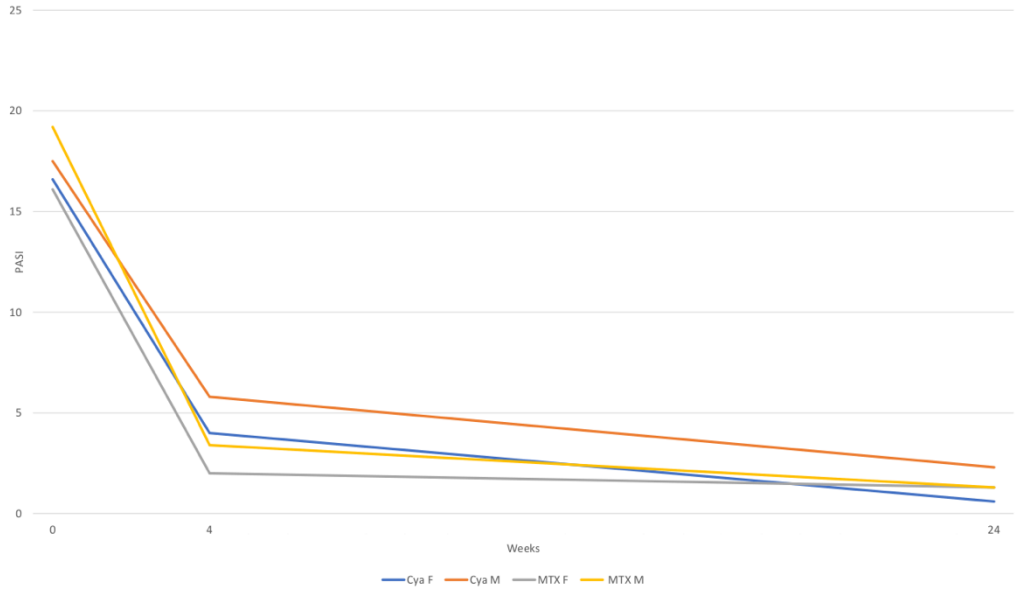
Table 1. Summary of demographic characteristics.

	Methotrexate (n=29)	**Cyclosporine (n=25)**
Age (years)	58.3	50
Gender (male:female)	19:10	14:11
Height (cm)		
Male	176.5	174.5
Female	164.9	165.5
Weight (kg)		
Male	84.3	80.3
Female	65.0	60.5
BMI		
Male	27.2	26.5
Female	24.2	25

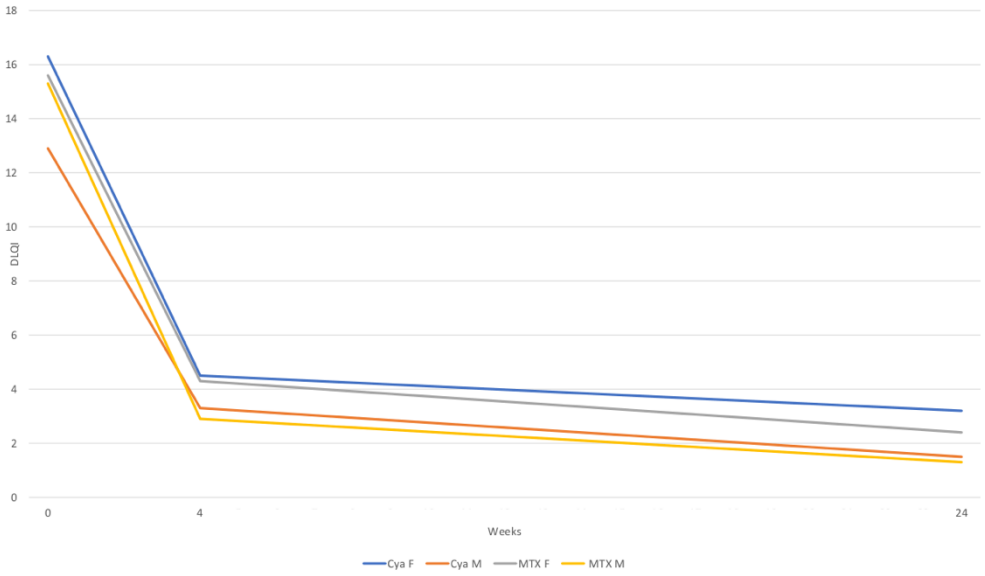
BMI, body mass index.

Figure 1. PASI score at baseline (T0), 4 weeks (T1), and 24 weeks (T2) after bimekizumab treatment initiation in male and female patients previously treated with cyclosporine or methotrexate.



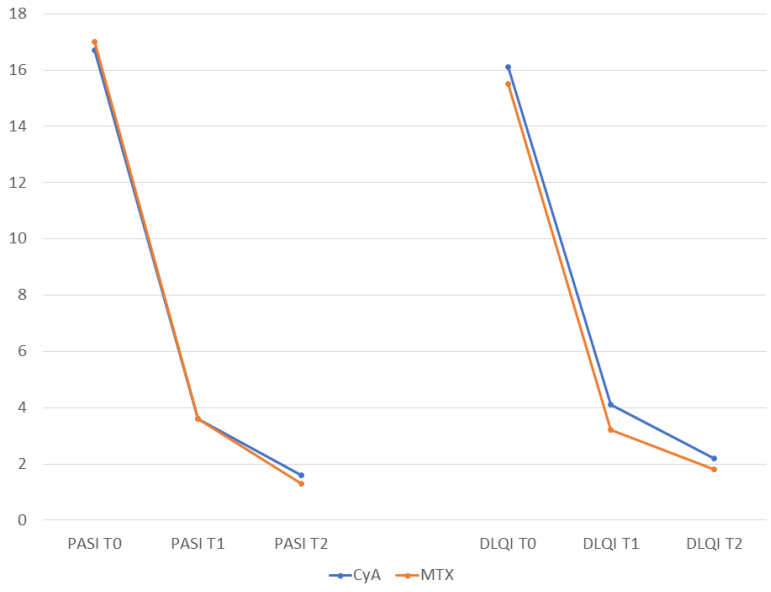
F, female; M, male; Cya, cyclosporine; MTX, methotrexate.

Figure 2. DLQI score at baseline (T0), 4 weeks (T1), and 24 weeks (T2) after bimekizumab treatment initiation in male and female patients previously treated with cyclosporine or methotrexate.



F, female; M, male; Cya, cyclosporine; MTX, methotrexate.

Figure 3. Change in PASI and DLQI scores over time at baseline (T0), 4 weeks (T1), and 24 weeks (T2) after bimekizumab treatment initiation in patients previously treated with cyclosporine or methotrexate.



CyA, cyclosporine; MTX, methotrexate.