



## Original Research

# Considerable variation among Iranian dermatologists in the knowledge and attitudes regarding the use of biologic agents to manage psoriasis <sup>☆</sup>



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## ABSTRACT

**Background:** Many international guidelines have been introduced with the aim of helping clinicians by providing evidence-based advice for the prescription of biologic therapies in psoriasis. Because no local or regional guideline is available, the treatment of psoriasis with biologics is mainly based on clinical experiences regarding the international guideline among Iranian dermatologists.

**Objective:** To assess the knowledge and attitudes among Iranian specialists regarding the use of biologic agents to manage psoriasis.

**Methods:** Data were collected using an electronic questionnaire specifically designed for this study based on a review of the literature. The designed Google form consisted of 53 multiple choice questions divided into five sections.

**Results:** A total of 111 dermatologists agreed to participate in this study. There was considerable variation among the responding dermatologists in terms of their knowledge and attitudes toward biologics. There were some significant associations between knowledge and attitudes of dermatologists toward biologics and their personal and professional characteristics.

**Conclusions:** More comprehensive educational approaches, both in the dermatology residency and post-graduation periods, could be very beneficial to promote the knowledge and attitude of the dermatologist in treating psoriasis with biologic agents. This study could be one of the first steps to develop a country-based or a region-based plan to improve the knowledge and attitude among dermatologists regarding the use of biologic drugs in psoriasis and possibly to reach a better status to prescribe these agents in the management of psoriasis.

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## Introduction

Psoriasis is a chronic, relapsing, immune-mediated skin disease affecting approximately 1 to 3% of the world population. Its profound impact on the emotional, social, and physical health of patients underlines the need for prompt, effective treatment with long-term disease control (Smith et al., 2009; Zamani et al., 2010). Several treatment options are available to treat this burdensome disease depending on the severity of the condition (Lynch

et al., 2014; Menter et al., 2008; Smith et al., 2009). The introduction of biologic therapy in dermatology in 2002 revolutionized the treatment of psoriasis in recent decades. These agents act by specifically targeting the immune cells underlying the pathology of psoriasis (i.e., T cells) by blocking cytokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) or interleukins (ILs) such as IL-17 and IL-23 (Feldman et al., 2015). Many international and even country-based guidelines have been introduced to help clinicians understand how to prescribe biologic therapies in psoriasis (Gottlieb et al., 2008; Hamadah et al., 2015; Ohtsuki et al., 2013; Puig et al., 2013; Smith et al., 2017). However, very few studies have addressed the true picture of how biologics are prescribed and whether dermatologists are aware of and follow the recommendations of these guidelines (Ara et al., 2011). On the other hand,

<sup>☆</sup> No human subjects were included in this study. No animals were used in this study.

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because the data on real-life treatment strategies could substantially differ from those in randomized controlled trials and guidelines, these observational studies can be of added value by enriching the body of evidence (Zweegers et al., 2016).

There are currently three biologic therapies licensed and commonly used by Iranian dermatologists as therapeutic options for psoriasis: infliximab, adalimumab, and etanercept. Because no local guideline is available, the treatment of psoriasis patients with biologics is mainly based on clinical experiences regarding the international guidelines or consensus. The present study was designed to assess variations in knowledge and attitudes among Iranian dermatologists about biologic therapy in psoriasis.

## Methods

### Subjects and data collection

A cross-sectional survey was undertaken among dermatologists practicing in public and private settings in Iran between August 2016 and February 2018. We sent invitations to participate in this survey via the social networks of dermatologists related to Iranian Society of Dermatology. Finally, 111 dermatologists agreed to participate in this study. The study was conducted in accordance with

the Declaration of Helsinki and was approved by the local ethics committee for medical research. The dermatologists were informed of the aims and methods to be used and the confidentiality of any data collected.

Data were collected using an electronic questionnaire specifically designed for this study based on a review of the literature. The designed Google form consisted of 53 multiple choice questions divided into five sections: (1) participants' demographic and professional characteristics (6 items); (2) knowledge and attitudes toward biologics in general (14 items); (3) infliximab-specific questions (11 items); (4) adalimumab-specific questions (11 items); and (5) etanercept-specific questions (11 items). The participants were provided with multiple choices for each question, and they were able to choose one or more choices for each question (Fig. 1).

### Statistical analysis

A descriptive analysis of all the study variables was carried out using the statistical package SPSS 24.0 for Windows. Categorical variables were summarized using the total number of cases in each category and the relative frequency compared with the total number of responses. Continuous variables were expressed as

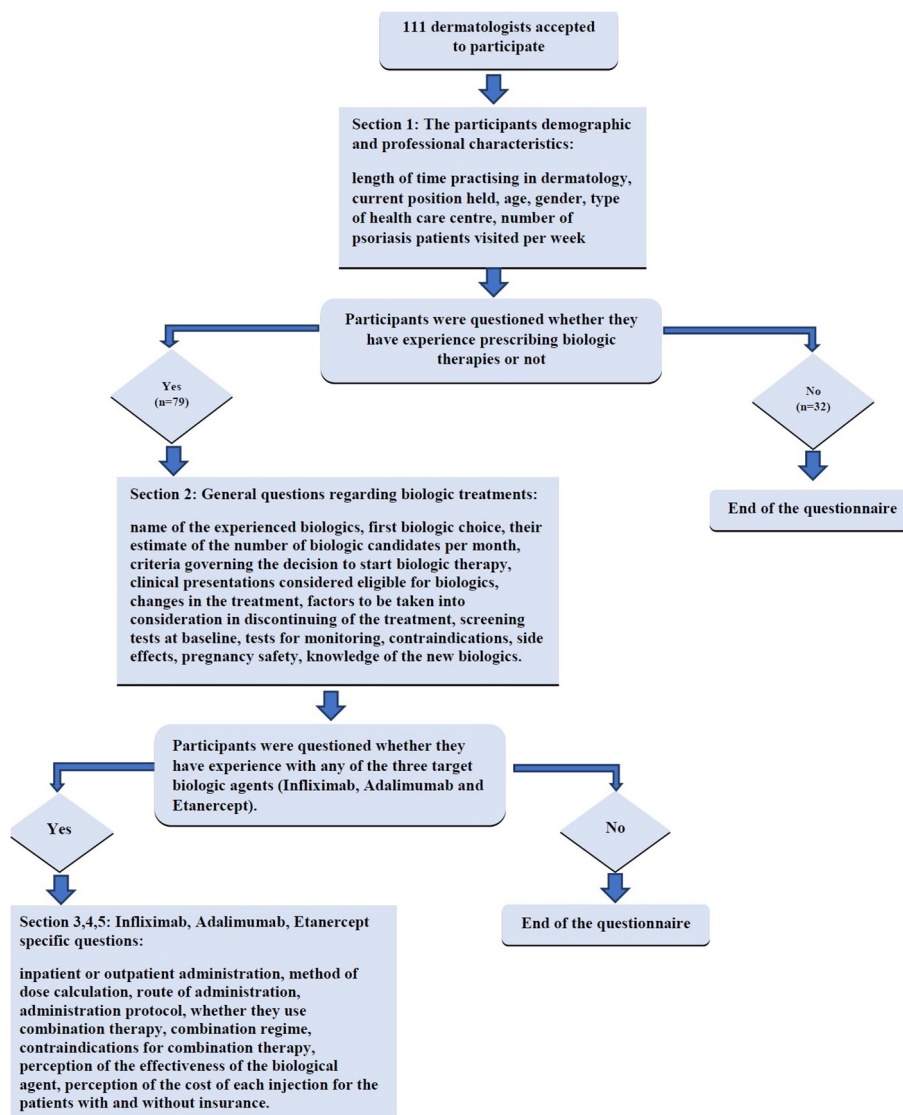


Fig. 1. Data collection methodology and questionnaire.

mean  $\pm$  standard deviation. A  $\chi^2$  for categorical variables and analysis of variance for continuous variables were used to identify the factors that were related to the answers to the questions. A  $p$  value  $<0.05$  was considered statistically significant.

## Results

### Characteristics of the respondents

Among the 111 dermatologists who agreed to participate in this study, 70 participants (63.1%) had experience prescribing biologic therapies and were eligible to complete the questionnaire. The mean age of these dermatologists was  $43 \pm 9.69$  years. Demographic and professional characteristics of the dermatologists were shown in Table 1.

### Knowledge and attitudes toward biologics

The biologics with which the respondents had the most clinical experience were infliximab (70%), etanercept (65.1%), and adalimumab (55.7%), respectively. Nearly all participating dermatologists (95.5%) were aware of the existence of the latest biologic therapies, including ustekinumab and secukinumab.

Whereas 44.9% of our sample dermatologists stated that their first biologic of choice differs in different clinical settings and depends on the patient's characteristics, the other half reported a preference to start with a particular treatment. The preference to start biologic therapy with infliximab was higher among the dermatologists who worked in public health care centers ( $p = .008$ ) and male specialists compared with female specialists ( $p = .04$ ). The majority of the surveyed dermatologists (88.2%) estimated that they start biologic treatment for fewer than five patients per month. The number of biologic candidates per month increased with an increasing number of psoriasis patients visited per week

( $p = .000$ ) among those who worked in public health care centers ( $p = .02$ ) and associate professors compared with other academic or nonacademic positions ( $p = .05$ ).

Among the respondents to the question about the criteria governing the decision to start biologic therapy, 10% reported the failure of topical treatments and phototherapy and 21.4%, 31.4%, and 51.4% prescribed one, two, and all available systemic therapies, including methotrexate, acitretin, and cyclosporin, respectively, before switching to biologics. However, 21.4% reported prescribing biologics regardless of the number of traditional systemic agents tried and when the duration to achieve a moderate improvement with the traditional therapies was more than 2 years. The patient's preference for more rapid remission of disease with biologic therapies was the reason behind choosing these agents for 58.6% of the dermatologists. The most common clinical presentation considered eligible for biologics was diffuse plaque psoriasis (95.7%), followed by severe psoriatic arthritis (79.7%).

Dermatologists were also asked to report the screening tests that they perform at baseline and the type of monitoring used during the treatment. The data varied significantly according to the characteristics of the respondents. There was a higher frequency of testing for Purified Protein Derivative (PPD) skin tuberculin test/Interferon Gamma Release Assay test (IGRA test) among younger practitioners ( $p = .02$ ) and chest radiograph among younger practitioners and those who worked in public health care centers ( $p < .05$ ); a higher frequency of cardiology consult among younger practitioners, those with less than 10 years of work experience or assistant professor academic positions, and those who worked in public health care centers ( $p < .05$ ); a higher frequency of testing for lipid profile among those with more than 20 years of work experience ( $p = .02$ ); a higher frequency of urinalysis testing among those with associate professor academic positions and those who worked in public health care centers ( $p < .05$ ); and a higher frequency of Erythrocyte Sedimentation Rate (ESR)/C-Reactive Protein (CRP) testing among older specialists and those with more than 20 years of work experience ( $p < .05$ ). Some screening and monitoring tests, including fasting blood sugar, lipid profile, urinalysis, chest radiograph, and stool examination, were requested less often by female dermatologists at baseline or during the treatment period ( $p < .05$ ).

The increased risk for developing sepsis (94.3%) and active tuberculosis (94.3%) were chosen by the largest proportion of the dermatologists as the main contraindications for the biologics. Concerning the side effects of the biologic agents, infection (82.4%) was chosen by the largest percentage of the respondents, followed by cardiac (60.3%) and autoimmune disorders (52.9%). However, male dermatologists considered the history of malignancy within past 5 years, high-grade congestive heart failure, and demyelination disorders more often as contraindications to starting biologics ( $p < .05$ ).

Biologic treatments were categorized as group B in pregnancy according to 47.8% of the dermatologists surveyed; however, the remaining dermatologists chose group C (24.6%), D (11.6%), and X (4.3%), and 11.6% stated that they did not know the pregnancy safety of these agents. The prevalence of choosing group B was significantly higher among male dermatologists and those with less than 20 years of work experience.

### Knowledge and attitudes toward infliximab, adalimumab, and etanercept

Most of the respondents reported that they would consider outpatient administration of adalimumab (94.9%) and etanercept (93.5%), whereas all the dermatologists surveyed stated they would use inpatient administration for infliximab. Subcutaneous injection was reported to be the technique of choice for

**Table 1**  
Demographic and professional characteristics of dermatologists ( $N = 70$ ).

Demographic characteristics	$n$ (%)
<b>Sex</b>	
Female	43 (61.4)
Male	27 (38.6)
<b>Work experience in dermatology</b>	
<10 years	41 (58.6)
10–20 years	21 (30)
>20 years	8 (11.4)
<b>Position</b>	
Professor	4 (5.7)
Associate professor	7 (10)
Assistant professor	16 (22.9)
No academic position	43 (61.4)
<b>Type of health care center*</b>	
Solo office <sup>†</sup>	39 (55.7)
Private skin clinics <sup>‡</sup>	22 (31.4)
Private hospitals	8 (11.4)
Public health hospitals <sup>§</sup>	44 (62.9)
<b>Psoriasis patients per week</b>	
<10	32 (45.7)
10–20	29 (41.4)
>20	9 (12.9)

\*Numbers may not add up to 70 and percentages may not add up to 100% because of the ability to choose more than one option as a workplace.

<sup>†</sup> In this type of office, only one dermatologist usually practices in the field of medical dermatology and sometimes cosmetic procedures.

<sup>‡</sup> In these clinics, a group of dermatologists practice together in different aspects of medical and procedural dermatology.

<sup>§</sup> These hospitals are usually managed and sponsored by governmental budget, and patients do not pay much if they have medical insurance.

administration of adalimumab (97.4%) and etanercept (97.8%), whereas 93.6% of the respondents agreed that they would use an intravenous infusion for infliximab.

Attitudes toward the use of combination therapy varied considerably among the dermatologists (Fig. 2). However, around 90% of the responders agreed that methotrexate is the drug of choice for combination therapy with all three biologics. With respect to other therapies considered unsafe for combination with biologics, the respondents mentioned live vaccines (79.5%), other biologic agents (34.1%), cyclosporine (27.3%), all vaccines (6.8%), and methotrexate (6.8%).

Overall, about half of the participants rated the efficacy of all three questioned biologics as between 50 and 70%. Assessment of the perception of the specialists about the cost of each injection indicated that although around 80% of the respondents were aware of the cost of injection with insurance, only 37.5%, 53.8%, and 39.5% were aware of the true cost without insurance of injection for infliximab, adalimumab, and etanercept, respectively. Male dermatologists were significantly more aware of the cost of adalimumab with insurance compared with female dermatologists.

## Discussion

Most of the existing guidelines recommend biologic therapy if systemic treatments such as methotrexate and cyclosporin have failed, are not tolerated, or are contraindicated. It is also recommended in generalized psoriasis, severe psoriasis in localized sites, and psoriasis with a large impact on the quality of life (Foulkes et al., 2011; Silveira et al., 2014; Smith et al., 2017). Most of the respondent Iranian dermatologists seem to follow these instructions. However, whereas more experienced dermatologists and those with a professor position prioritize the longevity of the previous treatments, the patient preference for better and more rapid improvement of skin lesions was considered as a more significant factor in choosing biologic agents by associate professors and specialists with 10 to 20 years of practice experience.

Screening tests at baseline and tests for monitoring varied significantly among the dermatologists according to their age, sex, work experience, position, and type of health center. It seems that male dermatologists and specialists who work in public health care centers tend to do more screening and monitoring tests. Although testing may seem innocuous, there are risks associated

with detecting false positives, leading to additional testing, morbidity, and additional health care cost and resources. Despite the lack of evidence to support routine monitoring, current guidelines recommend routine testing at baseline, which needs to be repeated every 3 and 6 months in case of clinical indications (Ahn et al., 2015; Doherty et al., 2008; Motaparthy et al., 2014; Nadkarni et al., 2018).

Based on currently available evidence, serious infections such as active tuberculosis, severe congestive heart failure, current malignant tumor, and previous or current demyelinating disease such multiple sclerosis are the four main contraindications for prescribing biologics (anti-TNF- $\alpha$  drugs) (Lee et al., 2018; Ohtsuki et al., 2013). Knowledge of these contraindications was significantly associated with the respondents' characteristics. Overall, it seems that younger practitioners, male dermatologists, those with academic positions, and dermatologists working in public health care centers are better informed of these contraindications. Biologics are class B in pregnancy, and most pregnancies reported in women taking a biologic therapy at conception and during pregnancy have successful outcomes (Galluzzo et al., 2018; Smith et al., 2017). However, less than half of the respondents in this survey answered this question correctly. The prevalence of choosing group B was significantly higher among male dermatologists and, surprisingly, those with less than 20 years of work experience.

Although monotherapy with biologics is highly effective in most patients with psoriasis, some patients do not show a proper response and require combination approaches for disease control. There is no approved indication for combining a biologic agent with a traditional systemic agent except for psoriatic arthritis (Lynch et al., 2014). Although most participating dermatologists in our study agreed that methotrexate was the drug of choice for combination therapy with all three mentioned biologics, they did not agree on choosing cyclosporine in combination with anti-TNF drugs. The highest preference for combining a biologic medication in the literature has also been expressed for methotrexate. It is followed by the combination of a biologic and acitretin and then a biologic and phototherapy combination (Armstrong et al., 2015). According to the available guidelines, combining cyclosporin with biologics should be done with caution because of the risk of leukoencephalopathy and deterioration of the immunocompromised conditions and increased risk of complications from serious infections (Ohtsuki et al., 2013).

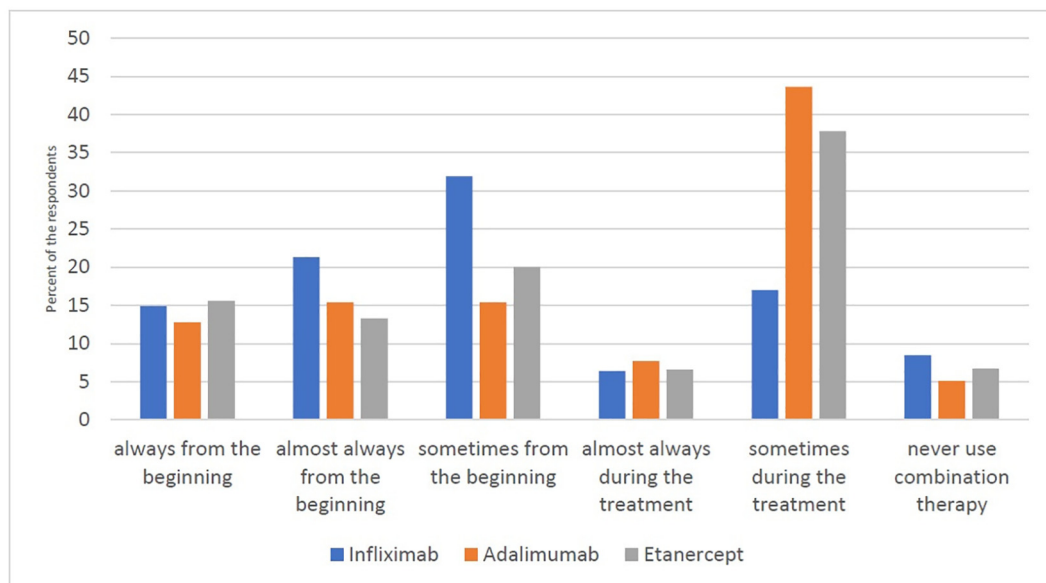


Fig. 2. Attitudes toward the use of combination therapy with three surveyed biologics among 70 dermatologists with experience to prescribe biologics.

In our study, only 63.1% of participants reported the experience of prescribing biologics in the treatment of psoriasis. This survey also revealed that there is considerable variation among the responding dermatologists regarding age, sex, and work experience in terms of knowledge of and attitudes toward the use of biologics in the treatment of psoriasis. These results are in accordance with our previous study, which reported a remarkable variation in attitudes toward methotrexate dosing and monitoring in the treatment of psoriasis (Zargari et al., 2014). These variations could in part be due to the personal, professional, and educational characteristics of the respondents. An important cause of the low engagement of Iranian dermatologists in using biologics was their high cost in the previous decade. The cost of these agents for each injection is about 25 to 30% of the average monthly income in Iran. After the production of biosimilars by Iranian pharmaceutical companies and their coverage by health insurance, the biologics are now more accessible for Iranian patients. Currently, biosimilars for anti-TNF agents are available in Iran (Jamshidi et al., 2017) and 90% of the cost is covered by insurance companies. Meanwhile, educational programs both for residents and dermatologists will encourage Iranian dermatologists to engage in the treatment of psoriasis with biologics. All these parameters should be considered to reach a possible unified local or even regional guideline or consensus on the use of biologic drugs in the treatment of psoriasis.

## Conclusions

Despite limitations such as a restricted number of respondent dermatologists and the heterogeneity of their age and educational profiles, our study can declare the need for more comprehensive educational plans regarding both the medical and health economy aspects on the use of biologics in psoriasis treatment. This study could be one of the first steps to development of a country-based or even region-based plan to improve knowledge and attitude among dermatologists on the use of biologic drugs in psoriasis and possibly to reach a better status to prescribe these agents in the management of psoriasis.

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## Conflict of Interest

None.

## Funding

None.

## Study Approval

The authors confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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