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Biologic and Targeted Therapy in the Treatment of Psoriasis – A Retrospective Study from a National Referral Center

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ABSTRACT Psoriasis is one of the most common chronic inflammatory skin disorders worldwide with a significant number of patients suffering from moderate to severe disease and requiring systemic therapy. Over the past two decades, better knowledge of disease pathophysiology has translated into treatment advances for both primary disease and its associated comorbidities. However, it is important to review the use of biologic or targeted therapy in a clinical setting in order to understand how to optimize therapeutic results and recognize any unmet needs in this patient subpopulation. We conducted a retrospective study on a cohort of patients diagnosed with psoriasis that had received at least one dose of biologic or targeted therapy for the treatment of psoriasis at the Rijeka Clinical Hospital Center. By documenting treatment trends and specific patient characteristics, we will be able to address any unmet needs in this patient population and provide individualized care strategies.

KEY WORDS: apremilast, biological therapy, interleukin-17 receptors, psoriasis, tumor necrosis factor-alpha

INTRODUCTION

Psoriasis is a complex multi-systemic chronic immune-mediated inflammatory disorder that affects approximately 2% to 3% of the general population regardless of sex, with an estimated 20% suffering from moderate to severe disease requiring systemic therapy (1,2). In particular, the prevalence of psoriasis in Croatia is estimated to be around 1.5%, which accounts for over 80 000 patients (3-5). Out of that number, close to 0.2% are treated with biologic or targeted therapy, thus emphasizing the need to regard psoriasis as a significant public health problem (3-5).

It is now widely recognized that patients with psoriasis have a higher rate of comorbidities compared with the general population. More specifically, current data suggests that it is the chronic inflammatory response coupled with production of Th1 and Th17 cytokines that promotes the systemic inflammation responsible for the high number of associated comorbidities in psoriasis (6-7). Nearly 30% of patients have concomitant psoriatic arthritis, while numerous studies, including those by Ahlehoff *et al.* and Li *et al.*, have shown that patients with psoriasis have

an increased risk of developing major cardiovascular disease (6-9). Studies also suggest a link between psoriasis and non-alcoholic fatty liver disease, with a prevalence of up to 60% (7,10). Thus, the chronicity of the disease coupled with numerous comorbidities leads to significant decrease in the quality of life, with an estimated 1 in 4 patients suffering from impaired long-term wellbeing (2,5).

Given the disease characteristics described above and the inevitable costs accrued with different treatment modalities, it is also important to recognize psoriasis as a disease with a high economic burden (2,11). More concretely, research conducted by Burgos-Pol *et al.* calculated the total annual cost per patient to range from close to 1800 euros to a little over 11500 euros (12).

Thus, given the complexity of this disease, a multidisciplinary therapeutic approach must be employed in order to tailor an effective treatment plan for each patient.

The key objectives of this study were to identify the prevalence of employed therapeutic modalities and treatment pathways in patients with moderate to severe psoriasis on biologic or targeted therapy; recognize treatment failures for that subset of patients; note the different reasons for drug termination; document time intervals for switching to another therapeutic agent; and identify cohort-specific comorbidities.

PATIENTS AND METHODS

This observational retrospective study was conducted through chart review and data extraction from the medical records at Rijeka Clinical Hospital Center, which has housed the Croatian National Referral Center for Psoriasis since 2005. The inclusion criteria used for this study included dermatologist-diagnosed patients with moderate to severe psoriasis who received treatment with at least one biologic or targeted therapy option. We collected data on the prevalence of employed biologic or targeted therapies, treatment failures, and consequent switches in treatment modality. Demographics and comorbidities were also identified.

RESULTS

The sample population consisted of 85 patients treated between January 2009 and December 2018 with a clinically and/or histologically confirmed diagnosis of moderate to severe plaque or pustular psoriasis. Additionally, patients must have received at least one dose of the following seven biologic or targeted therapies – infliximab, adalimumab, etanercept, ustekinumab, secukinumab, ixekizumab, and/or apremilast.

Table 1. Summary of comorbidities in patients with moderate to severe psoriasis on biologic and/or targeted therapy

COMORBIDITY	NUMBER OF PATIENTS
Psoriatic Arthritis	**48**
Dyslipidemia	**27**
Cardiovascular Disease	**23**
cardiac arrhythmia	7
ischemic heart disease	11
myocardial infarction	5
Arterial Hypertension	**19**
Non-alcoholic fatty liver disease	**17**
Gastrointestinal Disorders	**16**
gastritis	1
celiac disease	1
acute pancreatitis	1
Crohn's disease	1
irritable bowel disease	1
gastro-esophageal reflux disease	2
hernia operation	6
gallbladder removal	3
Infections	**16**
hepatitis A positive serology	4
hepatitis B positive serology	3
hepatitis C positive serology	1
latent tuberculosis	8
Obesity	**14**
Diabetes mellitus	**12**
Neoplasms	**10**
colon	3
uterine	2
prostate	2
breast	3
Allergic Diseases	**10**
angioedema	1
contact allergy	1
allergic asthma	2
nodular prurigo	2
rhinoconjunctivitis	2
severe drug allergy	2
Metabolic Syndrome	**7**
Vascular Diseases	**7**
deep vein thrombosis	4
stasis dermatitis	2
venous ulcer	1
Respiratory Disorders	**6**
pleural effusion	1
respiratory insufficiency	3
centrilobular emphysema	1
chronic bronchitis	1
Ophthalmologic Disorders	**5**
Kidney diseases	**4**
nephrolithiasis	3
renal insufficiency	1
Gynecological Disorders	**3**
Vitiligo	**3**
Central Nervous System Disorders	**3**
aneurism	1
stroke	1
migraine	1
Sideropenic anemia	**3**
Sjogren Disease	**2**
Auditory problems	**2**
Psychiatric Disorders	**2**

Overall, there was a higher proportion of men (57 men, 67.1%) compared with women (28 women, 32.9%). The age range for men was 25-77 years with

Table 2. Treatment pathways to biologic or targeted therapy

	INFLIXIMAB	USTEKINUMAB	ADALIMUMAB	SECUKINUMAB	APREMILAST	ETANERCEPT	IXEKIZUMAB
Phototherapy	3	10	9	2	10	5	2
Photochemotherapy	1	5	0	0	0	0	0
Phototherapy with systemic retinoids	0	1	1	0	3	2	0
Methotrexate	7	15	18	4	20	7	2
Acitretin	4	10	6	3	6	5	1
Cyclosporine	2	0	0	0	1	0	0
Biologic/targeted therapy as first-line systemic therapy	/	/	/	/	2	/	/

an average of 54 years, while the age range for women was 23-74 years with an average age of 53 years, and the median age was 57 years for both sexes.

Over half of all patients were diagnosed with concomitant psoriatic arthritis (56.5%), followed by dyslipidemia (31.8%), cardiovascular disease (27.1%), and arterial hypertension (22.4%). It is important to note that 8 patients (9.4%) were found to have positive QuantiFERON-TB Gold test results (7 patients prior to initiation of biologic therapy; 1 patient while on biologic therapy) indicating latent tuberculosis, and thus underwent a multi-month chemoprophylaxis regimen (Table 1).

As prescribed in the national guidelines, the obtained data indicates that the most common treatment pathway for patients in this cohort was to commence with topical agents such as corticosteroids, vitamin D3 derivatives or calcineurin inhibitors, followed by narrowband ultraviolet-B therapy (nbUVB) (48.24%), and/or photochemotherapy (7.06%), and then move on to systemic therapies such as methotrexate (85.88%), acitretin (41.18%), or retinoid-UVB (8.24%), and less often to cyclosporine (3.53%) in order to achieve adequate disease control (Table 2). When sustained disease control could not be achieved using conventional systemic therapies, the next step in the therapeutic pathway was to prescribe an appropriate biologic agent or targeted therapy option. Very seldomly was biologic or targeted therapy used as first-line therapy, with data revealing only a couple of patients (2 patients, 2.4%) commencing treatment with apremilast due to contraindications to conventional systemic therapies while having a Psoriasis Area Severity Index (PASI) average of 18.85 and Dermatology Quality of Life (DLQI) average of 20 points.

Prior to the initiation of biologic or targeted therapy, the patients' average PASI score was 25.33. A marked drop in PASI was noted following introduction of the initial biologic or targeted therapy, with 27 patients reaching PASI 100 response, 31 patients reaching PASI 90 response, and 20 and 7 patients reaching PASI 75 and PASI 50, respectively, within 12 to 28 weeks. Conversely, DLQI also showed significant improvement within the same timeframe, with patients averaging 16 points beforehand and 5 points afterwards.

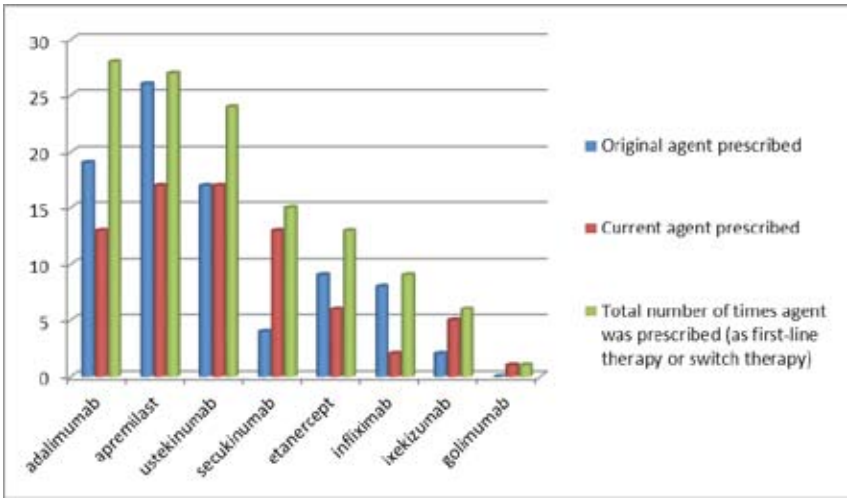
Overall, 38 patients reached PASI 100 at some point in the course of the study timeframe, with the majority of them being on ustekinumab (10 patients), adalimumab (9 patients), or secukinumab (8 patients); 38 patients reached PASI 90 mostly on apremilast (11 patients), adalimumab (10 patients), or ustekinumab (6 patients); 8 patients reached PASI 75 with the top three agents being apremilast (4 patients) followed closely behind by adalimumab and etanercept (2 patients each); and PASI 50 was maintained by 1 patient on apremilast. It should also be noted that DLQI dropped further among the patient cohort with an average of a little under 2 points when evaluated later in time during the course of the study.

Data collected in the study showed that the largest portion of patients began therapy with a tumor necrosis factor alpha (TNF-α) inhibitor (36 patients, 42.4%), followed by phosphodiesterase 4 inhibitor apremilast (26 patients, 30.6%), while other anti-cytokines such as interleukin 12/interleukin 23 and interleukin 17 inhibitors accounted for the least amount of patients (23 patients, 27.1%) (Table 3).

Overall, adalimumab (32.9%) was the most commonly prescribed biologic agent, followed closely by apremilast (31.8%) and ustekinumab (28.2%), while infliximab (10.6%) and ixekizumab (7.1%) were among the least prescribed (Table 3).

Through the course of the study timeframe, 32 patients (37.7%) terminated (switched or discontinued) the original biologic or targeted therapy agent within an average of 28 months. Furthermore, 8 patients (9.4%) terminated the second-line treatment, while 4 patients (4.7%) and 1 patient (1.2%) terminated the

Table 3. Prescription of biologic or targeted therapy



third- and fourth-line treatment, respectively. There was also a shortening of switch intervals as the number of biologic agents per patient increased. Namely, the average switch interval between the second and third biologic agent was 17 months, while switching to a fourth or fifth biologic agent occurred at an average of 10 and 3 months, respectively.

Apremilast was noted as having the highest treatment termination rate (10 patients, 11.8%) and the shortest switch interval (5 months) when used as first-line therapy. In contrast, etanercept and ustekinumab were the two agents that showed the lowest termination rate when used as first-line therapy (3 patients, 3.5% and 5 patients, 5.9%, respectively) while exhibiting the longest switch interval (42 months).

In terms of overall prescription and termination rates, the obtained data showed that patients on ustekinumab had the longest switch interval with an average of 37 months, followed closely behind by etanercept (35 months) and infliximab (28 months). On the other side of the spectrum, secukinumab, apremilast and ixekizumab had a switch interval of up to 6 months. Analyzing the data even further indicates that although adalimumab (11 patients) and apremilast (10 patients) had a similar number of patients terminate therapy, the average number of months on each drug differed drastically and was 27 months and 5 months, respectively (Table 4).

Extracted data indicated that adalimumab was the preferred second-line therapy option, while third-line

Table 4. Treatment termination overview

TREATMENT TERMINATION (N=NUMBER OF TIMES BIOLOGIC WAS PRESCRIBED)	INFLIXIMAB n=7	USTEKINUMAB n=6	ADALIMUMAB n=2	SECUKINUMAB n=10	APREMILAST	ETANERCEPT	IXEKIZUMAB	TOTAL NUMBER
Primary failure			1	1	7	1	1	11
Secondary failure	3	4	4	1	1	2		15
Adverse Reaction	4	2	5		2	2	1	16
Personal Reason			1			1		2
DURATION OF TREATMENT PRIOR TO TREATMENT TERMINATION					1		1	2
0-3 MONTHS			3	2	7	2		14
3-6 MONTHS	2	2	1		2	1	1	9
6-12 MONTHS	3	2	3			2		10
1-3 YEARS	2	1	4			1		8
3-6 YEARS		1				1		2
AVERAGE DURATION OF TREATMENT TERMINATION (MONTHS)	28	37	27	6	5	35	5	

therapy did not show prevalence of any one agent over another. Moreover, even though multiple transition pathways were noted, the most prevalent switch was that of infliximab to adalimumab (6 patients, 15.8%) followed by adalimumab to secukinumab (5 patients, 13.2%).

Lastly, the main reason for termination was due to adverse events (36.4%), followed by secondary failure which included the development of anti-drug antibodies and loss of therapeutic effectiveness (34.0%), primary failure (25.0%), and treatment termination due to personal reasons (4.5%) (Table 4).

As of last follow-up, most patients were on apremilast and ustekinumab (17 patients, 23.0% each), followed closely behind by secukinumab and adalimumab (13 patients, 17.6% each), etanercept (6 patients, 8.1%), ixekizumab (5 patients, 6.8%), infliximab (2 patients, 2.7%), and lastly golimumab (1 patient, 1.4%). Overall, of the patients lost in long-term follow-up, 3 patients transferred treatment to a different institution, 6 patients actively terminated treatment due to either personal reasons or drug side-effects, with 1 patient reverting back to conventional systemic therapy, and 1 patient passed away due to causes not related to treatment of his primary disease.

DISCUSSION

Multiple biologic agents and targeted therapy options have become licensed and are thus available in Croatia for the treatment of psoriasis and psoriatic arthritis since 2008, when Peternel *et al.* documented the first two patients successfully treated for psoriasis as a primary disease (13).

According to the current Croatian guidelines for the diagnosis and treatment of psoriasis, biologic therapy is indicated in patients with moderate to severe (chronic plaque) psoriasis who have failed to show sufficient improvement, did not tolerate, or had contraindications towards at least two different systemic treatment options including photochemotherapy, retinoids, cyclosporine, and/or methotrexate (4).

Furthermore, in Croatia PASI >15 and/or Body Surface Area (BSA) >15% and/or DLQI >15 is required in order to initiate biologic therapy, which is not completely in alignment with the European guidelines that recommend PASI/BSA/DLQI of >10 (4-5,14). As with most other countries, the assessment of treatment effect is required at week 12 (and week 28) following biologic therapy initiation. Likewise, maintenance therapy is allowed for patients who reach a response of ≥50% reduction in PASI and ≥5 points improvement in DLQI (4).

This highlights the fact that regulatory health insurance eligibility criteria regarding the coverage of biologics, the total health expenditure per capita which is approximated around 500 euros in Croatia, and available charitable programs, are important factors that influence treatment decisions and in turn therapy prescription behavior in Croatia (5).

Although its effectiveness in psoriasis has proven moderate, apremilast, a phosphodiesterase-4 inhibitor, has a high rate of prescription because it seems to provide the most convenience for patients. The trifecta of minimal laboratory monitoring, the appeal of an oral drug, and suitability for most patients make apremilast a good first-line therapy option when conventional systemic therapy is either contraindicated or ineffective (15,16).

With the number of TNF-α inhibitors available nowadays, it may be difficult to navigate through choosing the right agent for the right patient. In these cases, it is imperative to evaluate patient characteristics, such as the presence of comorbidities or age, and weigh them against potential risks. While etanercept may be a better choice for pediatric patients and younger women who may become pregnant, patients with Crohn's disease may benefit from adalimumab (15).

Lastly, even though interleukin-17 inhibitors such as secukinumab and ixekizumab may have the potential for better results when compared with the older biologics, currently available data does suggest that secukinumab may cause upper respiratory infections and even exacerbate Crohn's disease, while data for ixekizumab is scarce due it being approved for the treatment of psoriasis as recently as 2016 (15,17,18).

Even though biologics have revolutionized the management of psoriasis since 2004, when etanercept became the first biologic agent registered by the European Medicines Agency, we must acknowledge that there is a subset of patients who do not achieve or maintain a sufficient response to biologic treatment. The data collected identified one such patient, undergoing four switches with an average switch interval of 4 months without demonstrating satisfactory disease control. Additionally, eight patients underwent two switches, and four patients underwent three switches. In such cases, it is important to consider including additional topical therapy, phototherapy, methotrexate, increasing the dose of the biologic agent, or even shortening the time period between doses in order to optimize treatment before drug termination.

The main limitations of our study include geographical bias, since the study was conducted at

a single clinical center, and that the data collected reflected prescription patterns under the premise that patients adhered to therapy. Nonetheless, since the study was conducted at the national referral center, we are confident that the results adequately reflect the overall patterns of psoriasis management in Croatia.

CONCLUSION

Documenting the use of biologic and targeted therapy over a ten-year timeframe has enabled us to gain more concrete knowledge about this specific Croatian subpopulation that will in turn result in improved individualized care.

References:

1. Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. Br J Dermatol. 1996; 135:533-7.
2. Gulliver WP, Randell S, Gulliver S, Gregory V, Nagle S, Chambenoit O. Biologic therapy utilization in patients with moderate to severe psoriasis and psoriatic arthritis: an observational summary of biologic therapy use in a clinical setting. J Cutan Med Surg. 2018;22:567-76.
3. Barisic-Drusko V, Paljan D, Kansky A, Vujasinovic S. The prevalence of psoriasis in Croatia. Acta Derm Venereol Suppl (Stockh). 1989;146:178-9.
4. Kaštelan M, Puizina-Ivic N, Ćeovic R, Jukić Z, Bulat V, Simonić E, *et al.* Guidelines for the diagnosis and treatment of psoriasis. Lijec Vjesn. 2013; 135:195-200.
5. Rencz F, Kemeny L, Gajdacsi JZ, Owczarek W, Arenberger P, Tiplica, GS, *et al.* Use of biologics for psoriasis in Central and Eastern European countries. J Eur Acad Dermatol Venereol, 2015;29, 2222-30.
6. Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic arthritis and burden of disease: Patient perspectives from the population-based multinational assessment of psoriasis and psoriatic arthritis (MAPP) survey. Rheumatol Ther. 2016;3: 91-102.
7. Oliveira Mde F, Rocha Bde O, Duarte GV. Psoriasis: classical and emerging comorbidities. An Bras Dermatol. 2015;90:9-20.
8. Ahlehoff O, Gislason GH, Charlot M, Jørgensen CH, Lindhardsen J, Olesen JB, *et al.* Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. J Intern Med. 2011;270:147-57.
9. Li WQ, Han JL, Manson JE, Rimm EB, Rexrode KM, Curhan GC, *et al.* Psoriasis and risk of nonfatal cardiovascular disease in U.S. women: a cohort study. Br J Dermatol. 2012;166:811-8.
10. Miele L, Vallone S, Cefalo C, La Torre G, Di Stasi C, Vecchio FM, *et al.* Prevalence, characteristics, and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol. 2009;51:778-86.
11. Fowler JF, Duh MS, Rovba L, Buteau S, Pinheiro L, Lobo F, *et al.* The impact of psoriasis on health care costs and patient work loss. J Am Acad Dermatol. 2008;59:772-80.
12. Burgos-Pol R, Martinez-Sesmero JM, Ventura-Cerda JM, Elias I, Caloto MT, Casado MA. The cost of psoriasis and psoriatic arthritis in 5 European countries: a systematic review. Actas Dermosifiliogr. 2016;107:577-90.
13. Peternel S, Prpić-Massari L, Guina T, Novak S, Brajac I, Kaštelan M. Treatment of severe psoriasis with infliximab: report of two cases. Acta Dermatovenerol Croat. 2009;17:204-6.
14. Nast A, Gisondi P, Ormerod AD, Saiag P, Smith C, Spuls PI, *et al.* European S3-Guidelines on the systemic treatment of psoriasis vulgaris—Update 2015--Short version--EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29:2277-94.
15. Cather JC, Young M, Bergman MJ. Psoriasis and Psoriatic Arthritis. J Clin Aesthet Dermatol. 2017;10:S16-25.
16. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, *et al.* efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase iii, randomized controlled trial (esteeM 2). Br J Dermatol. 2015;173:1387-99.
17. Thaci D, Blauvelt A, Reich K, Tsai TF, Vanaclocha F, Kingo K, *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: Clear, a randomized controlled trial. J Am Acad Dermatol. 2015;73:400-9.
18. Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, *et al.* Phase 3 trials of ixekizumab in Moderate-to severe Plaque Psoriasis. N Engl J Med. 2016;375:345-56.