A retrospective study on drug survival of biologics among patients with psoriasis seen in tertiary hospital in Johor Malaysia

Mazliha Mashor[1], AdvMDerm(UKM), Kit Wan Wong[2], AdvMDerm(UKM), Kwee Eng Tey[2], MRCP, Siew Eng Choon[2], FRCP

[1]Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia, [2]Department of Dermatology, Hospital Sultanah Aminah, Johor Bahru, Malaysia

ABSTRACT

Introduction: Limited information exists regarding drug survival of biologics among psoriasis patients in Malaysia. This study aimed to determine the drug survival of biologics in Malaysian psoriasis patients, the reasons for drug discontinuation and to identify the predictor of drug survival.

Materials and methods: A retrospective review of case notes on adult psoriasis patients treated with biologics in Hospital Sultanah Aminah Johor Bahru Malaysia, between January 2006 and December 2020. Drug survival was analysed using the Kaplan–Meier method.

Results: By December 2020, 100 patients with 154 treatment courses of biologics were included in the study. Male to female ratio was 1:1. The mean age at onset was 31.36 ± 11.72 years. Ustekinumab was the most frequently prescribed biologics (39%), followed by adalimumab (29.2%), secukinumab (14.9%), etanercept (13%), and infliximab (3.2%). Overall median drug survival for biologics was 25 months (interquartile range [IQR]= 12.0–.0). The median drug survival for ustekinumab was 35 months (IQR, 12–93); followed by 25 months (IQR, 12.0–), 18 months (IQR, 7–85), 17 months (IQR, 11–43), and 8 months (IQR, 1-10) for secukinumab, adalimumab, etanercept, and infliximab, respectively. The main reason for drug discontinuation was loss of efficacy (26%), inadequate funding (14.3%), loss to follow-up (10.4%), adverse events (4.5%), and patients' request (1.3%).

Conclusion: Our study shows ustekinumab has the best long-term drug survival among biologics in Malaysian patients with psoriasis in real-life setting. Further study is required to evaluate the long-term drug survival for newer biologics.

KEYWORDS:
Biologics, drug survival, psoriasis, treatment

INTRODUCTION

Psoriasis is a common chronic relapsing immune-mediated disease. Its prevalence was reported to be higher in countries with high income and older population, whereas the prevalence is relatively lower in Asian countries.[1] Malaysian clinical practice guidelines on management of psoriasis vulgaris recommended biologics if patients fulfil the following criteria: severe disease [body surface area ≥30% or Psoriasis Area and Severity Index (PASI) ≥20] and not responding, intolerant to, or having contraindications for conventional systemic treatment or phototherapy.[2]

Although clinical trials focus on efficacy and safety of the biologics, the enrolled subjects might be relatively different from those in daily practice due to the presence of stringent inclusion and exclusion criteria.[3,4] In choosing a practical tool that reflects the real-life setting, drug survival has been a useful instrument to measure the clinical success of biologics in psoriasis treatment. Drug survival is described as the time from initiation of biologic therapy to discontinuation.[5-7] In reality, drug survival is influenced by numerous factors, including efficacy, safety, patient's satisfaction, compliance, and physician preference. Specifically, median drug survival is frequently measured, indicating the length of time in which half of biologics are switched or stopped, whilst another half are still being administered.[8,9]

To date, limited information exists regarding drug survival of biologics amongst psoriasis patients in Malaysia. Our objective is to determine the drug survival of biologics, the reasons for drug discontinuation and to identify the predictor of drug survival in Malaysian psoriasis population.

MATERIALS AND METHODS

This retrospective study was done by reviewing the electronic records of all psoriasis patients who were treated with at least one biologics in the dermatology clinic of Hospital Sultanah Aminah Johor Bahru Malaysia till 31 December 2020. The following information was extracted: age at psoriasis onset and biologic initiation, gender, ethnicity, body weight, body mass index (BMI), prior systemic treatment before biological initiation (such as phototherapy, methotrexate, ciclosporin, acitretin), use of concomitant methotrexate while on biologic, presence and absence of psoriatic arthritis, type of psoriasis (namely chronic plaque psoriasis, pustular psoriasis, and erythrodermic psoriasis), comorbidities (includes high blood pressure, diabetes mellitus, and dyslipidaemia), PASI score on treatment initiation, and

This article was accepted:
Corresponding Author: Mazliha Mashor
Email: ammz83@yahoo.com

reasons for treatment discontinuation. Based on World Health Organization (WHO) Asian classification, BMI 23–27.49 and BMI ≥ 27.5 indicate overweight and obesity, respectively. During the study period, tumour necrosis factor inhibitors (TNF)-α (include infliximab, etanercept, adalimumab), interleukin-12/23p40 inhibitor (ustekinumab), and interleukin-17 inhibitor (secukinumab) were analysed. The study was approved by the Ministry of Health Institutional Review Board and Medical Research ethics committee (NMRR-19-732-47165).

Statistical analysis

The demographic data were analysed using descriptive data. Results were expressed as number (n) and percentage (%). Descriptive statistics are presented as counts and percentages for categorical variables. Mean with standard deviation (SD) was used for normally distributed data while median with interquartile range (IQR) was used for data which were not normally distributed. Categorical variables were compared using chi-square analysis. All statistical analyses were performed using SPSS software version 22.0 (IBM Corp, Armonk, NY, USA). Drug survival was analysed using the Kaplan–Meier method. Cox proportional hazard model for multivariate analysis was applied to identify any associated predictor for drug survival such as patient age, gender, biologic therapy naïve status, and concomitant methotrexate. P-value <0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

Overall, 100 patients were included in the study and their characteristics were summarized in Table I. The mean duration between disease onset and first administration of biologics was 10.70 ± 8.51 years. The male to female ratio was 1:1. Chronic plaque psoriasis was the most common type of psoriasis (83%), followed by erythrodermic psoriasis (26%) and pustular psoriasis (14%). Psoriatic arthritis was present in almost half of the study patients (49%). Interestingly, a significantly higher proportion of patients with psoriatic arthritis were prescribed with adalimumab compared to other biologics (p=0.00). Mean baseline PASI score before biological initiation was 18.4 ± 17.1. In total, 154 treatment series were evaluated during the study period. Ustekinumab was the most frequently prescribed biological treatments (39%), followed by adalimumab (29.2%), secukinumab (14.9%), etanercept (13%), infliximab (3.2%), and golimumab (0.6%). The mean administration period of biologics was 29.07 ± 29.83 months. Notably, one-third of the patients (33%) were taking concomitant methotrexate while on biologic treatment.

Drug survival

Regarding the drug survival analysis of the biologics, we have evaluated 153 treatment courses. The Kaplan-Meier survival curves were demonstrated in Figure 1(a-c). This analysis excluded one patient with both severe chronic plaque psoriasis and psoriatic arthritis who received golimumab treatment as the fourth biologic from rheumatologist after failure to respond to several TNF-α inhibitors including etanercept, infliximab, and adalimumab. The median drug survival in all patients was 25 months (IQR=12.0–85.0). Analysis of drug survival for individual biologics revealed statistically significant differences (log rank test p = 0.003). The estimated median drug survival for individual biologic was 35 months (IQR, 12–93) for the ustekinumab group, followed by 25 months (IQR, 12 –) for secukinumab, 18 months (IQR, 7–85) for adalimumab, 17 months (IQR, 11–43) for etanercept, and 8 months (IQR, 1–10) for the infliximab. Among the biologically naïve patients, the overall median drug survival was 24 months (IQR, 12–85). The drug survival of individual biologic in the biologic-naïve was as follows: 35 months (IQR, 12–93) for ustekinumab, 19 months (IQR, 16–50) for etanercept, 18 months (IQR, 7–85) for adalimumab, 12 months (IQR, -) for secukinumab and 1 month (IQR, 1.0–1.0) for infliximab. On the other hand, the median drug survival in biologic experienced patients was 29 months (IQR, 8.0-). The drug survival of individual biologic in the biologic-experienced was 52 months (IQR, 20 –) for ustekinumab, 13 months (IQR, 6–) for adalimumab, 9 months (IQR, 8–13) for etanercept, and 8 months (IQR, 1–10) for infliximab. It might be difficult to estimate accurately the drug survival in secukinumab cohort, as it was commercialised much later than other biologics. Multivariate analysis using Cox regression showed parameters such as age, gender, obesity, comorbidities, previous phototherapy, presence of psoriatic arthritis, biologic naïve status and concomitant methotrexate administration were not shown to significantly influence drug survival (Table II).

Reason for discontinuation

Out of 100 patients, 59 patients were still undergoing treatment at the end of the study, whereas 41 patients discontinued biologic therapy as shown in Table III. The main reason for drug discontinuation was loss of efficacy (26%), followed by inadequate funding (14.3%), loss to follow-up (10.4%), adverse events (4.5%), and patients' request (1.3%). The loss of efficacy was seen highest for adalimumab (12.8%). Inadequate funding was found specifically for ustekinumab (11.4%). Adverse events occurred mainly in 7 patients (4.5%) who were on TNF-α inhibitors. Infliximab treatment caused infusion reaction in two patients and *Escherichia coli (E Coli)* sepsis in one patient. Adalimumab was associated with adverse events in four patients including two patients with latent tuberculosis infection (LTBI), one patient with cerebrovascular accident, and another one with cutaneous squamous cell carcinoma. Prior to adalimumab administration, tuberculosis (TB) screening was negative for both patients with LTBI. They were found to have positive tuberculin skin test after 1 year of adalimumab and both subsequently completed the treatment for LTBI. One individual opted to discontinue etanercept because she was planning to conceive. Cessation of treatment was revealed in four patients after reaching sufficient improvement while on biologic.

DISCUSSION

To the best of our knowledge, this is the first study of real-world data collected over the period of more than 10 years to compare drug survival of biologics among Malaysian psoriatic patients. The overall median drug survival of all

Table I: Demographic and clinical characteristics of study population

Characteristics		n=100	Etanercept (n=15)	Infliximab (n=1)	Adalimumab (n=27)	Ustekinumab (n=46)	Secukinumab (n=11)	*p* value
Age (years, mean ± SD)	At onset	31.36 ± 11.72	33 ± 8.19	32.00 ±	31.11 ± 11.406	31.17 ± 13.578	30.45 ± 9.62	0.86
	At starting biologic	40.83 ±12.12	47.93 ± 10.33	42.00±	38.11 ± 12.79	40.72 ± 14.22	38.18 ± 10.79	0.989
Gender (n, %)	Male	52	7 (13.5%)	0	12 (23.1%)	27 (51.9%)	6 (11.5%)	0.605
	Female	48	8 (16.7%)	1 (2.1%)	15 (31.3%)	19 (39.6%)	5 (10.4%)	
Ethnicity (n, %)	Malay	43	5 (11.6%)	1 (2.3%)	15 (34.9%)	19 (44.2%)	3 (7.0%)	0.648
	Chinese	42	7 (16.7%)	0	10 (23.8%)	20 (47.6%)	5 (11.9%)	
	Indian	15	3 (20.0%)	0	2 (13.3%)	7 (46.7%)	3 (20.0%)	
Baseline weight (kg)		62.48 ± 30.06	67.13 ± 25.00	47.00 ±	61.22 ± 33.50	61.02 ± 30.62	66.73 ± 29.04	0.187
BMI (mean ± SD)		27.41 ±7.53	28.64 ± 7.06	21.00 ±	28.16 ± 7.56	26.95 ± 7.96	27.25 ± 7.07	0.616
Baseline PASI (mean ± SD)		25.57 ± 15.40	31.29 ± 11.81	7.00 ±	7.00 ± 21.22	25.30 ± 13.16	26.68 ± 13.28	0.08
Comorbidities (n, %)	Obesity	22	4 (18.2%)	0	6 (27.3%)	9 (40.9%)	3 (13.6%)	0.937
	Diabetes mellitus	20	5 (25.0%)	0	6(30.0%)	6 (30.0%)	3 (15.0%)	0.44
	Arterial hypertension	20	7 (35.0%)	0	5 (25.0%)	6 (30.0%	2 (10.0%)	0.079
	Dyslipidaemia	2	1 (50.0%)	0	0	1 (50.0%)	0	0.650
Psoriatic arthritis (n, %)		49	14 (28.6%)	0	18 (36.7%)	11 (22.4%)	6 (12.2%)	0.00
Prior treatment (n, %)	Phototherapy (NBUVB)	32	8 (25.0%)	0	4 (12.5%	16 (50.0%)	4 (12.5%)	0.110
	Methotrexate	83	11 (13.3%)	1(1.2%)	25 (30.1%)	39 (47.0%)	7 (8.4%)	0.200
	Ciclosporin	46	6 (13.0%)	0	12 (26.1%)	23 (50.0%)	5 (10.9%)	0.845
	Acitretin	45	7 (15.6%)	1(2.2%)	15 (33.3%)	20 (44.4%)	2 (4.4%)	0.223
Concomitant use of methotrexate (n, %)		33	6 (18.2%)	1 (3.0%)	12 (36.4%)	13 (39.4%)	1 (3.0%)	0.122

n, total number of biologic

Table II: Cox regression analyses. Hazard ratio for risk treatment discontinuation of etanercept, infliximab, adalimumab, ustekinumab, and secukinumab

Variable	HR	95% Confidence interval	*p* value
Age onset > 30	1.025	0.989–1.062	0.181
Female gender	1.383	0.678–2.825	0.373
Concomitant psoriatic arthritis	1.622	0.673–3.910	0.281
Obesity	0.538	0.259–1.117	0.096
Diabetes	0.717	0.208–2.470	0.598
Arterial hypertension	2.171	0.591–7.974	0.243
Dyslipidaemia	2.769	0.391–19.597	0.308
Previous phototherapy	1.665	0.748–3.706	0.212
Biologic naïve patients	0.656	0.064–6.688	0.722
Concomitant methotrexate	1.271	0.618–5.957	0.514

Table III: Reasons for treatment discontinuation of the treatment series with biologics

	Loss of efficacy n (%)	Adverse events n (%)	Loss to follow up n (%)	Inadequate funding (n, %)	Patient request (undisclosed reason) n (%)	Adequate improve-ment n (%)	Other: pregnancy n (%)	Continue n (%)	Total n (%)
Etanercept	13 (8.5 %)	0	4 (2.6 %)	0	0	0	1 (7%)	2 (1.3 %)	20 (13.1 %)
Infliximab	2 (1.3 %)	2 (1.3 %)	0	0	0	1 (0.7 %)	0	0	5 (3.3 %)
Adalimumab	18 (11.8 %)	5 (3.3 %)	6 (3.9 %)	0	1 (0.7 %)	1 (0.7 %)	0	14 (9.2 %)	45 (29.4 %)
Ustekinumab	7 (4.6 %)	0	6 (3.9 %)	16 (10.5 %)	1 (0.7 %)	1 (0.7 %)	0	29 (19 %)	60 (39.2 %)
Secukinumab	0	0	0	6 (3.9 %)	0	1 (0.7 %)	0	16 (10.5 %)	23 (15 %)
Total	40 (26.1%)	7 (4.6%)	16 (10.5)	22 (14.4)	2 (1.3)	4 (2.6)	1 (0.7)	61 (39.9)	153 (100%)

n, total number of biologic courses for each biologic.

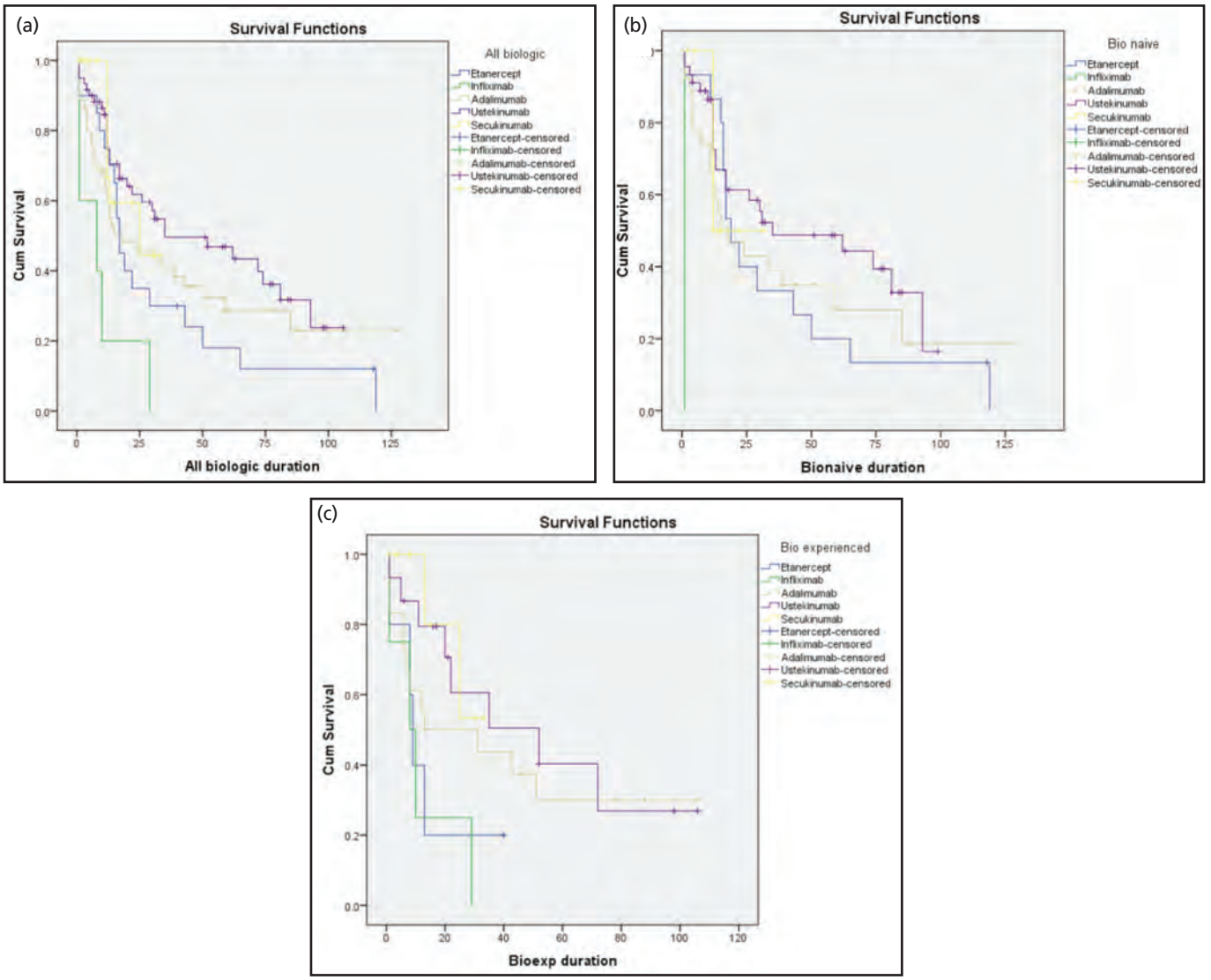

Fig. 1: (a) Kaplan–Meier plot of drug survival for all biologics. (b) Kaplan–Meier plot of drug survival for each biologic in the biologic-naïve. (c) Kaplan–Meier plot of drug survival for each biologic in the biologic-experienced.

biologics in our study was 25 months. This duration is comparable to study conducted in a single-centre Japanese series by Ohata et al[3] (25.5 months), but shorter than the duration of drug survival reported by Vilarrasa et al.[10] (31 months), Shalom et al. (27.9 months).[7] Majority of the literature published revealed ustekinumab has the longest drug survival rate among all biologics.[11,12] A systematic review by No et al.[9] reported that ustekinumab had much longer drug survival beyond 5 years when compared to TNF-α inhibitors. A meta-analysis by Liu et al suggested that ustekinumab is associated with the superior drug survival in all and biologic-naive subjects.[13] The reason for lower rate of discontinuation with ustekinumab compared to TNF-α inhibitors is likely attributed to multiple factors such as greater efficacy, favourable side effect profile, and low immunogenicity.[9] Injection site reactions were the least commonly observed in ustekinumab-treated patients. In addition, the improvement of treatment compliance is expected in patients who receive ustekinumab due to the less frequent (3 monthly) dosing regimen.[11,14,15] With regards to biologic-experienced cohort, a previous study by Cozzani et al[8] discovered that ustekinumab has less remarkable drug survival data which might be explained by the possibility of alteration in the immune system which further reduce the effectiveness of subsequent biologics. Interestingly, our analysis found that ustekinumab has greater survival in both naive and non-naive patients, and this finding is similar to the report by Menter et al.[11]

Several studies have demonstrated that female gender is considered to be negative predictors of drug survival.[10,16-18] Another study by Jacobi et al[19] revealed patients with psoriatic arthritis had longer drug survival, while those with metabolic syndrome were associated with loss of treatment retention. Previous report found that patients with concomitant methotrexate treatment have a superior drug survival rate, and this observation is thought to be associated with reduction in the formation of drug autoantibodies.[16] On

the contrary, our study did not demonstrate any significant influence of gender, obesity, comorbidities, psoriatic arthritis, biologic naive status, and concomitant methotrexate on the drug survival in the treated population.

Reason for discontinuation- Loss of efficacy

In our study, loss of efficacy was the most common reason for biologic discontinuation which is consistent with other studies.[9,11] A meta-analysis by Lin et al demonstrated ustekinumab is the biologic least frequently discontinued due to diminished efficacy, whereas etanercept is terminated most commonly following the same reason.[13] In contrast, our study revealed loss of efficacy was seen highest for both adalimumab (12.8%). The exact mechanism that causes the treatment failure is not completely understood. Immunogenicity of biologics was hypothesized to play a role in the diminished clinical response and this is illustrated by the formation of antidrug antibodies resulting in immune complexes interrupting drug interaction or bioavailability.[9,20] Interestingly, past report showed that ustekinumab stimulates fewer antidrug antibodies than TNF-α inhibitors which might explain the lower rate of discontinuation of ustekinumab.[8,21]

Reason for discontinuation- Lack of funding

Inadequate funding was the second most common reason of drug termination in our cohort, in keeping with the previous report by Choi et al.[22] In our study, four patients have paid for biologics out of their own pocket. A study on cost-effectiveness analysis of psoriasis treatment in Malaysia revealed biologic regimen has the highest effectiveness but requires the highest cost (estimated around RM54 000 or US$16 000 for 6 months duration) and that itself comprises about two-third of the overall medication cost.[23] There are different regulations on biologic funding being implemented between every country which may indirectly reflect the prescription trend of biologics.[22] Result from a study by Youn et al indicated that all patients in Korea have public health insurance, while considerably lower coverage (63%) of public health insurance were depicted in other Asia-Pacific countries including Malaysia.[24] The substantially high cost of biologics is considered one of the major contributing factor of drug discontinuation for ustekinumab in South Korea, particularly when the treatment is not reimbursed.[22] Regardless of efficacy of biologic treatment, treatment compliance may become a concern if patients have to postpone the treatments past the recommended schedule in order to reduce the cost.[24] In Malaysia, the funding for biologic is limited and in some cases, the reimbursement are not sustainable for longer than 6 months to 1 year. Regrettably, psoriasis become worsen in these group of patients once they discontinue their treatment following insufficient funding.

Reason for discontinuation- adverse events

In our cohort, ustekinumab is the least likely to be discontinued due to adverse effects, similar to previous reports.[13,25,26] Drug discontinuation due to adverse events occur in seven patients who have been on TNF-α inhibitors. We found that infliximab caused infusion reaction in two patients and *E. coli* sepsis in one patient in our cohort. Previous studies have found that among biologic-naïve subjects infliximab has the lowest overall drug survival specifically related to the adverse effects.[13,26–28] According to the study by Yiu et al, infliximab was linked to increase risk of serious infections when compared with conventional systemic therapies.[29] On the other hand, LTBI was associated with two asymptomatic patients who received adalimumab in our study. Both patients completed anti-tuberculous treatment without any major complication. A systematic review and meta-analysis by Zhang Z et al[30] suggested that the risk of developing tuberculosis is doubled whenever patients are receiving TNF-α inhibitors. A review by Fabroni et al highlighted that TNF-α inhibitors might predispose patients to the severe variants of tuberculosis predominantly extrapulmonary tuberculosis and disseminated tuberculosis.[31] Therefore, it is prudent to screen patients for latent or active tuberculosis infection before commencing TNF-α inhibitors and to consider starting anti-tuberculous prophylaxis if tested positive. Meanwhile, periodic assessment is required to identify any symptoms and/or signs of tuberculosis infection when patients receive ongoing biologics treatment. Based on the evidence available, most psoriasis patients with positive tuberculosis screening were less likely to receive TNF-α inhibitors. Instead, prescribing other type of biologics such as IL-12/23 and IL-17 inhibitor are considered to be more reasonable as the risk of tuberculosis while on these biologics is considered low.[32,33] A report by Sbidian et al[34] recommends that young individuals having chronic or latent infection such as hepatitis B infection or history of tuberculosis may consider ustekinumab as alternative treatment option. Currently, the use of relatively newer biologics such as IL-23 inhibitor might need further study to determine the drug safety especially for those with infection risk.

LIMITATION

Our study had some limitations. Firstly, this is a single-centre retrospective study and the subjects were not randomised to different treatments. Furthermore, the existing data on the biologics were heterogenous due to the differences in timing of availability and commercialization of the various biologics.

Secondly, the prescribing pattern in daily practice could be influenced by some degree of selection bias. In our study, the numbers of patients on ustekinumab and adalimumab in our analyses were considerably higher than those on etanercept and infliximab. This practice is unavoidable because certain treatments are selected according to cost, efficacy, safety profile, ease of administration as well as preferences of the clinicians and patients which reflect real-world practice.

Thirdly, we did not have adequate data on drug survival of newly available biologics in the market. Future study is needed to evaluate the long-term drug survival for the comparatively newer biologics such as interleukin-17 and interleukin-23 inhibitor.

CONCLUSION

Our study demonstrated that ustekinumab has the highest long-term drug survival among all biologics in Malaysian

patients with psoriasis in real-life setting. Further study is required to evaluate the long-term drug survival for newer biologics including interleukin 23 inhibitor. These findings are useful references for clinicians to consider in the selection of biologics for psoriasis treatment in daily clinical practice.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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