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ORIGINAL ARTICLE

A Case Series Exploring the Efficacy, Secondary Failure, Paradoxical Event & Relapse with Ustekinumab Therapy in Chronic Plaque Psoriasis

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ABSTRAK

Ustekinumab adalah agen biologi yang berkesan untuk rawatan kulit psoriasis dengan menyasarkan molekul interleukin 12 dan 23. Namun begitu ada beberapa halangan ketika penggunaannya seperti kegagalan sekunder dan juga peristiwa paradoks. Penyakit juga didapati kembali menyerang selepas terapi dihentikan. Kajian kohort retrospektif telah dilakukan ke atas pesakit kulit kronik psoriasis yang telah menerima ustekinumab di antara tahun 2013 ke 2018 di Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM). Demografi, ciri-ciri klinikal, keberkesanan rawatan, komplikasi, kadar dan corak penyakit berulang dikaji melalui rekod-rekod pesakit. Enam (75%) pesakit adalah lelaki. Enam (75%) pesakit ini tidak pernah menerima agen biologi sebelum ini. Usia median pesakit adalah 41.5 tahun (IQR 26.8-48.3), tempoh median penyakit ialah 16.5 tahun (IQR 6.5-23.0). Tempoh median untuk mencapai kadar 75% pengurangan penyakit (PASI75) adalah 16 minggu. PASI75 pada minggu ke 12 dicapai oleh 37.5% pesakit manakala tempoh median untuk mencapai sekurang-kurangnya PASI75 adalah 16 minggu. Tempoh median keseluruhan rawatan adalah selama 102 minggu. Semua pesakit berjaya dirawat. Dua (25%) pesakit mengalami kegagalan sekunder. Seorang (12.5%) pesakit mendapat peristiwa paradoks dengan tumbuhnya fenomena nanah dan plak di kulit semasa rawatan. Tempoh median untuk penyakit berulang adalah 40 minggu. Semua pesakit kecuali seorang memerlukan rawatan biologi untuk penyakit berulang. Ustekinumab berkesan untuk semua pesakit. Kejayaan rawatan diperolehi 4 minggu selepas piawai yang dijangkakan. Kohort ini telah merekodkan kegagalan sekunder dan fenomena paradoks yang jarang berlaku. Penyakit didapati akan berulang dan corak psoriasis yang berbeza ditemui selepas

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rawatan dihentikan.

Kata kunci: agen biologi, psoriasis, ustekinumab

ABSTRACT

Ustekinumab is an anti-IL12/23 biologic agent used for treatment of psoriasis with excellent efficacy. However, there are therapeutic obstacles such as secondary failure and paradoxical event. Disease relapse upon discontinuation of therapy is common. A case series was performed on patients with chronic plaque psoriasis who received ustekinumab between 2013 to 2018 at a tertiary referral centre. Demographics, clinical characteristics, duration of therapy, efficacy, treatment complications, rate and pattern of relapses were determined from the patients' medical records. Out of 8 patients, 6 (75%) patients were males. There were 6 (75%) biologic-naïve patients. Median age was 41.5 years (IQR26.8-48.3), median duration of psoriasis was 16.5 years (IQR6.5-23.0). Median duration to achieve Psoriasis Activity and Severity Index (PASI)75 was 16 weeks and median total duration of treatment was 102 weeks. All patients achieved treatment success. PASI75 at week 12 was achieved by 37.5%, a median of 16 weeks was required to achieve at least PASI 75 but 6 (75%) attained PASI 90 by then. One patient (12.5%) developed paradoxical event with pustular and plaques. Secondary failure occurred in 2 (25%) patients. All patients relapsed after treatment discontinuation, relapse occurred at median of 40 weeks. Most (71%) developed plaques on relapse but 25% developed plaques and pustules. All but one patient required further biological agent for treatment of relapse. Ustekinumab was efficacious in all patients. Treatment success was achieved slightly later than standard duration. The rare occurrences of secondary failure and paradoxical were observed. Relapse was inevitable, new onset pustular eruptions featured in relapses.

Keywords: biologics, psoriasis, ustekinumab

INTRODUCTION

Psoriasis is a chronic immune-mediated disease with cutaneous and joint involvement that affect 0.91-8.5% of the world's population (Parisi et al. 2013). Cardiovascular disease and the metabolic syndrome are common and important systemic associations (Choon et al. 2014; Kimball et al. 2008; Smith et al. 2017) The effect of the disease on patients' quality of life is well documented (De Korte et al. 2004).

Biological agents marked an important milestone in psoriasis therapy. Their efficacies are comparable or superior than conventional systemic therapies, with very good safety profiles.

Conventional systemic therapies such as methotrexate, acitretin and cyclosporine are limited by various serious adverse effects including bone marrow suppression, dyslipidaemia, liver cirrhosis, pulmonary fibrosis, hypertension and renal impairment (Choon et al. 2014; Kimball et al. 2008). Indications for biological agents in chronic plaque psoriasis are patients with severe disease that have failed or are contraindicated for systemic agents (Choon et al. 2014; Smith et al. 2017), or diseases with significant impact on physical, psychological, or social functioning (Smith et al. 2017).

Ustekinumab is a fully human IgG monoclonal antibody against interleukin (IL)-12 and IL-23 (Benson et al. 2011). Ustekinumab is among the first line of biologics recommended in many chronic plaque psoriasis guidelines (Choon et al. 2014; Menter et al. 2011; Ohtsuki et al. 2013; Smith et al. 2017). Psoriasis Area and Severity Index or PASI is accepted worldwide as a tool to assess severity of plaque psoriasis by assessing three domains clinically which include thickness of plaques, erythema and scale thickness (Chalmers 2015). Sixty to seventy percent of patients achieved target response by 12 weeks (Menter et al. 2011; Ohtsuki et al. 2013; Smith et al. 2017). Adverse events including injection site reactions were comparable to placebo (Leonardi et al. 2008). While the efficacy and safety of biological agents including ustekinumab are well documented, other therapeutic issues like secondary failure, paradoxical event and relapse are limited to case reports and case series. Biological agents are reserved for patients with severe psoriasis and complicated management history in our clinical setting as usage is limited by the high cost of these medications. We report our experience using ustekinumab for psoriasis in a case series involving 8 patients treated at a tertiary referral centre in central Malaysia to highlight therapeutic obstacles of secondary failures, paradoxical events and relapses.

MATERIALS AND METHODS

A retrospective case series was performed. We reviewed the medical records of patients who received ustekinumab for chronic plaque psoriasis between 2013 to 2017 in Dermatology Clinic, Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Data on demography, clinical characteristics, duration of ustekinumab therapy, rate of disease clearance, rate of relapse and pattern of relapse were recorded. Treatment success was defined as achieving PASI75 (at least 75% reduction of PASI from baseline) at week 12 (Menter et al. 2011; Smith et al. 2017). PASI is well recognised psoriasis severity assessment tool. Severity of plaque psoriasis is determined by clinical assessment of three domains; thickness of the plaques, erythema and scale (Chalmers 2015). Minimal response criteria was defined as PASI at least 50 from baseline (Smith et al. 2017). Relapse meant loss of PASI after stopping treatment (Menter et al. 2011). Time to relapse was defined as time to lose PASI50 (Menter et al.

2011). Secondary failure occurred when PASI50 was initially achieved PASI50 but the response was lost with time and ongoing treatment (Smith et al. 2017).

RESULTS

Eight patients were treated with ustekinumab during the study period. Six were males (75%), 2 females (25%) with median age of 41 years (IQR26.8-48.3). Median duration of psoriasis was 16.5 years (IQR6.5-23.0). Ustekinumab dose was prescribed according to standard dosing protocol of subcutaneous 45 mg subcutaneous injections at week 0, 1, and 4, followed by every 12 weeks. The dose for one patient was increased to 90 mg starting from week 12 as he weighed almost 100 kgs with severe erythrodermic psoriasis. Six (75%) patients had chronic plaque psoriasis, 25% have pustular psoriasis while 2 (25%) had psoriatic arthropathy. Six (75%) patients were biologic naïve and two (25%) had psoriatic arthropathy.

Patient 1

A 50-year-old male with 20 years history of chronic plaque psoriasis. Narrowband UVB phototherapy (NBUVB) failed to achieve satisfactory response. Other previous treatments included ciclosporin (completed 1 year), methotrexate with cumulative dose approaching 4 gm and acitretin. Baseline PASI was 14.8. PASI90 was achieved by week 16 and his total treatment duration was 105 weeks. Psoriasis relapsed 40 weeks post ustekinumab, with plaques and minimal pustules.

Patient 2

A 46-year-old male had chronic plaque psoriasis for 25 years. Acitretin and methotrexate (cumulative dose 1.5 g) was complicated by transaminitis. He had received ustekinumab for a total of 52 weeks with good response. The second course of ustekinumab was commenced 40 weeks after discontinuation of the first course with baseline PASI of 15 and DLQI of 18. Psoriasis was well controlled by 12 weeks. However, he developed secondary failure at 52 weeks with PASI of 12.2 and DLQI of 16. Methotrexate was added for combined therapy without much improvement. Ustekinumab was later switched to secukinumab.

Patient 3

A 38-year-old male with chronic plaque psoriasis and psoriatic arthropathy (PsA) of 4 years duration. He had been treated with few biological agents including etanercept, adalimumab and ustekinumab with good response. However, treatment were interrupted due to limited funding. Ciclosporin caused hypertension, methotrexate caused hepatitis and he failed NBUVB. His baseline PASI was 54.6 and DLQI was 24. PASI75 was achieved after 4 weeks of ustekinumab therapy. PASI90 was achieved with quiescent PsA at 52 weeks. Ustekinumab was maintained for 2 years. Chronic plaque psoriasis and PsA flared 26 weeks off therapy.

Ustekinumab was then restarted.

Patient 4

A 29-year-old male had 14 years history of chronic plaque psoriasis. Methotrexate caused transaminitis. His baseline PASI was 70.5. PASI90 was achieved after 17 weeks of ustekinumab therapy which was maintained for 41 weeks. Relapse with plaque psoriasis occurred after 65 weeks of stopping ustekinumab. He was subsequently treated with secukinumab.

Patient 5

A 44-year-old male had guttate and pustular psoriasis for 4 years. He experienced acitretin induced hepatitis and periungual granuloma. There was poor response to methotrexate. He achieved PASI75 at week 42 with baseline PASI of 65.3 following ustekinumab therapy. Ustekinumab was continued for 123 weeks. Relapsed of psoriasis occurred at week 66 week.

Patient 6

A 26-year-old female developed chronic plaque psoriasis at the age of 8 years. She had methotrexate induced lung fibrosis and cyclosporine induced hypertension and hypercholesterolaemia. Her baseline PASI was 14.3. She achieved PASI100 at week 16. Unfortunately, she developed paradoxical pustular psoriasis with 1% body surface area covered with pustules and plaques at week 24 week. There were no other identifiable triggers for the eruptions. She responded well to topical corticosteroid. She received 77 weeks of ustekinumab. Plaques reappeared after 28 weeks of ustekinumab discontinuation, requiring re-commencement of treatment.

Patient 7

A 49-year-old female had psoriasis for the past 24 years. She had pustular psoriasis which later developed into severe chronic plaque with psoriatic arthropathy. NBUVB was ineffective with poor response to acitretin, and methotrexate caused bicytopenia. Baseline PASI was 20.3. PASI75 was achieved after 4 weeks of ustekinumab. She developed secondary failure at week 44 despite being a biologic naïve patient. She is now on secukinumab.

Patient 8

A 21-year-old male had concurrent chronic plaque psoriasis and atopic eczema of 15 years. He was treated with ciclopsorin for 2 years, his eczema went into remission but he developed severe psoriasis flare. Methotrexate therapy was complicated by transaminitis. Prior to ustekinumab, his baseline PASI was 22.4. He achieved PASI90 at week 16. He was still on ustekinumab 12 weekly with duration of treatment of 140 weeks at the time of data collection. Table 1 summarised the patients' demographic and clinical characteristics.

PASI75 or treatment success was achieved at week 12 by 3 (37.5%) of our patients. A median of 16 weeks therapy was required to achieve at

Table 1: Demographic and clinical characteristics of the patients.

ID	Age/Sex/ Ethnicity	Type of Psoriasis	PsA	Disease duration (years)	Co-morbidities	Biologic naive	Previous treatment	
							Photo	Systemic
1	50/M/C	Ps	No	20	Dyslipidaemia Hypertension Latent TB	Yes	Yes	CsA MTX Acitretin
2	46/M/C	Ps	No	25	Dyslipidaemia Fatty liver	No	Yes	MTX Acitretin
3	38/M/I	Ps	Yes	4	Dyslipidaemia Hypertension Fatty liver Latent TB	No	No	CsA MTX
4	29/M/M	Ps	No	14	Obesity Dyslipidaemia	Yes	Yes	MTX
5	44/M/M	Pustular → Ps	No	4	Dyslipidaemia Hypertension	Yes	No	MTX Acitretin
6	26/F/M	Ps	No	18	Exogenous Cushing Dyslipidaemia	Yes	No	CsA MTX
7	49/F/C	Pustular → Ps	Yes	24	IHD Dyslipidaemia Hypertension T2DM ESRF	Yes	Yes	MTX Acitretin
8	21/M/M	Ps	No	15	Atopic Dermatitis Hypertension Fatty liver	Yes	Yes	CsA MTX

Photo=pthototherapt; Ps=psoriasis; PsA=psoriatic arthritis' IHD=ischaemic heart disease' T2DM=type II diabetes mellitus; CsA= cyclosporine; MTX= methotrexate

least PASI75 however 6 (75%) patients showed excellent response where PASI90 was attained. The median total duration of treatment were 102 weeks with relapse occurring at a median of 40 weeks. All patients relapsed and required re-commencement of a biological agent except for patient 1 whom was treated with acitretin. Disease duration (r=0.47, p=0.24), PASI at week 0 (r=-0.24, p=0.57), and treatment duration (r=0.36, p=0.43) were not identified as risk factors for relapse. Interestingly 2 (25%) patients with chronic plaque psoriasis relapsed with development of both plaque and pustular types of psoriasis. Secondary failure was seen in 2 (25%) patients whilst on ustekinumab at week 52 and 44 weeks, the latter patient was a biologic-naïve patient. Paradoxical event with mild pustules and plaques was observed in 1 (12.5%) patient. It was successfully controlled with topical corticosteroids without requiring discontinuation of ustekinumab. There were no other major or minor adverse events experienced by our patients. Table 2 showed an overview of the therapeutic regimes, response, relapse and treatment following ustekinumab discontinuation among our patients.

Table 2: Therapeutic regimes, response, relapse and treatment following discontinuation of ustekinumab.

ID	PASI week 0	Rx regime: 45 mg at 0, 4, & every 12 weeks	Treatment success (week 12)	PASI 75 (week)	PASI 90 (week)	Rx duration (week)	Time to relapse (week)	Type of relapse	Rx post relapse
1	14.8	Yes	No	16	16	105	40	Plaque & localised pustular	Acitretin
2	15	Yes	Yes	12	12	77	Secondary failure week 52		Secukinumab
3	54.6	Yes	Yes	4	50	120	26	Plaque	Ustekinumab
4	70.5	Yes	No	17	17	41	65	Plaque	Secukinumab
5	65.3	45 mg x2, 90 mg 12 weekly	No	42	52	123	66	Plaque	Secukinumab
6	14.3	Yes	No	16	16 Paradoxical flare	77	28	Plaque & GPP	Ustekinumab
7	20.3	Yes	Yes	4	16	102	Secondary failure week 44		Secukinumab
8	22.4	Yes	No	16	16	Treatment continued			

GPP=generalised pustular psoriasis

DISCUSSION

All of our patients showed improvement with ustekinumab therapy. However, PASI75 achieved at our centre by week 12 were lower if compared to at least 59.5% as reported by landmark trials (Griffiths et al. 2010; Igarashi et al. 2012; Leonardi et al. 2008; Kim et al. 2008; Tsai et al. 2011). Instead our PASI75 or higher were achieved by median of week 16. The delay may be due to severe disease (median PASI 21.4, IQR14.9-62.6 at baseline) and most patients had difficult to treat and recalcitrant psoriasis with failures to other systemic therapies.

Psoriasis relapses were observed in all our patients following discontinuation of ustekinumab. Disease duration, psoriasis severity and ustekinumab treatment duration were not multiple co-morbidities is a factor that may have contributed to higher risk of relapse. All patients have dyslipidaemia, most had concomitant hypertension (5, 62.5%) and fatty liver (3, 37.5%). These diseases contribute to systemic inflammation which affects psoriasis therapy (Kimball et al. 2008). A non-significant longer durability of therapeutic effect has been documented with longer treatment duration (Ko et al. 2009; Tsai et al. 2011). Our patients received longer total duration of treatment, and relapses occurred later compared to ACCEPT (Griffiths et al. 2010) with total treatment duration of 52 weeks and relapses recorded at 18 weeks. Relapses at 22 weeks after 40 weeks of ustekinumab therapy were reported by

Kamaria et al. (2018). All of our patients except one required re-treatment with biological agent following their relapse.

We were not able to find data on type of relapse in literature. Most of our patients developed plaques but interestingly a quarter of them developed pustules for the first time. Systemic corticosteroid withdrawal is well recognised to precipitate pustular psoriasis. Chronic plaque psoriasis transformed to pustular type due to unstable, active inflammatory process caused by abrupt corticosteroid dose reduction or discontinuation (Benjegerdes et al. 2016). However, the pustules appeared much later than that induced by corticosteroids which typically occurred between 4-8 weeks.

Secondary failure was observed in our biologic naïve and biologic experienced patients. Secondary failure has been associated with development of antidrug antibody (ADA) with a prevalence of 3.8-6% (Hsu et al. 2014). Anti ustekinumab antibody (AUA) were found in patients with minimal response at 36-52 weeks of therapy (Chiu et al. 2014; Hsu et al. 2014; Kim et al. 2008). We were unable to test for AUA and serum ustekinumab due to limited resources. Anti-nuclear antibody (ANA) positivity has also been associated with higher risk of secondary failures (Griffiths et al. 2010). ANA were negative both pre and post treatment in our patients. Concomitant use of methotrexate reduced the risk of secondary failure while on anti -tumour necrosis factor α agents (anti-TNFα) (Hanauer et al. 2004; Toussirot & Aubin 2016). However, this is not the case for ustekinumab as its pharmacokinetics are unaffected by simultaneous use of methotrexate (Harrison et al. 2009).

Our case series captured occurrence of paradoxical event which is rarely reported with ustekinumab, despite our small number patients. Paradoxical event is more commonly associated with anti-TNFα therapy in patients with rheumatoid arthritis (Hanauer et al. 2004; Toussirot & Aubin 2016), chronic plaque psoriasis, ankylosing spondylitis and inflammatory bowel disease (Harrison et al. 2009). The cutaneous eruptions reported were mainly pustular but includes chronic plaques and guttate psoriasis (Toussirot & Aubin 2016). TNF-α inhibitors induced or exacerbate psoriasis in 127 patients, where palmo-plantar pustular psoriasis accounted for 40.5% while plaque-type psoriasis occurred in 33.1% (Ko et al. 2009). Pustules localised to the legs developed after 9 days of ustekinumab, treatment was changed to golimumab (Dai & Chen 2018). Both plaques and pustules occurred after 10 and 4 weeks of treatment respectively in another 2 patients (Caca-Biljanovska et al. 2013; Hay & Pan 2014). Topical treatment was successful without the need to withdraw ustekinumab (Caca-Biljanovska et al. 2013) while a more widespread disease required switching of the biologic agent to adalimumab (Hay & Pan 2014). Palmo-plantar eruptions occurred after 6 weeks of ustekinumab treatment that required a change of therapy to cyclosporine in another patient (Suh et al. 2018). Based upon the experiences of all of these authors, therapy and

Table 3: Summaries of paradoxical events compared with current literatures

Sudy	Age/ sex	Type of Psoriasis	Time to onset	Clinical presentations	Area affected	Treatment	Stop Ustekinumab
Gregoriou et. al. (Gregoriou et. al. 2019)	54/F	Ps & PsA	2 days	Erythema & yellow pustules	Trunk & limbs	Mtx	Yes
Wenk et. al. (Wenk et. al. 2012)	37/F	Ps & PsA	4 days	Annular & erythematous desquamating plaques & pustules	Generalised	Topical & systemic corticosteroid Acitretin	Yes
Caca-Biljanovska et. al (Caca-Biljanovska et al. 2013)	34/F	Ps	10 weeks	Annular erythematous plaques & pustules	Trunk & limbs	Topical corticosteroid	No
Hay & Pan (Hay & Pan 2014)	47/M	Ps & PsA	4 weeks	Erythematous plaques & pustules	Generalised	Adalimumab	Yes
Suh et al. (Suh et al. 2018)	30/M	Ps	6 weeks	Numerous pustules	Palms & Soles	Topical corticosteroid CsA	Yes
Dai & Chen (Dai 2018)	70/M	Ps	9 days	Pustules on erythematous base	LL bilaterally	Acitretin	No
UKM Medical Centre	26/M	Ps	24 weeks	Pustules & plaque	Trunk	Topical corticosteroid	No

decision to discontinue ustekinumab depended on the clinical severity of the paradoxical event while the choice of alternative therapy varies. Table 3 summarised the characteristics of paradoxical events reported in the literature and subsequent management of the patients. The postulated pathophysiology of paradoxical events are chemokine disequilibrium and gene polymorphism (Seneschal et al. 2009). Inhibition of IL-23 may indirectly cause increase in IFN α that promote T-cell activation indirectly via myeloid dendritic cell, or directly through IFN α sensitive T cells (Chan et al. 2006; Nestle & Gilliet 2005). IFN α also stimulates expression of chemokine T-cell receptors leading to aberrant expression of T-cells and neutrophils causing the paradoxical eruption (Elliott et al. 2009; Friedrich et al. 2014). IL36 receptor antagonist mutation is thought to be involved as it is well recognised in inducing generalised pustular psoriasis (Wang et al. 2016). Interpretation of our results are limited by the small number of patients and should not be generalised. The subjects were a group of patients with severe psoriasis, multiple comorbidities and complicated management history. However, they represent the typical patients that are treated with biological

agents in our country.

CONCLUSION

Ustekinumab was efficacious, PASI75 as the therapeutic target was achieved but treatment success took slightly longer. All patients failed to maintain disease remission after discontinuation of ustekinumab therapy, relapse was rapid and almost all patients required further biological therapy. Pustular relapse was observed in patients without history of pustular lesions. Secondary failures and paradoxical event were captured in our small case series despite its rarity.

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