INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder that affects approximately 1-3% of the general population.\(^1\) Patients with severe psoriasis that impairs their quality of life require aggressive treatment. The use of conventional treatments such as retinoids, methotrexate or cyclosporine is often limited by organ toxicity. For this reason, the advent of biologic treatment was revolutionary in psoriasis therapy. Although dermatologists currently have several choices of biologics, the optimal treatment against psoriasis has not yet been determined. Approximately 30% of patients show an insufficient response to biologics.\(^2,3\) In addition, some patients still encounter adverse effects (AE), such as infusion reactions, drug eruption or infections. Patients with a suboptimal response or AE are usually switched to other biologics; however, relatively few studies have examined the efficacy of changing biologics in these situations.\(^4-9\) Identifying prognostic factors associated with treatment discontinuation would greatly aid in predicting the efficacy of the first agent and in assessing the risk of adverse events.

Honda et al concluded that switching to a second biologic therapy to address the first’s inefficacy or adverse events often results in significant improvement in moderate to severe psoriasis.\(^10\) According to Bayaraa, biologic reagents were changed mostly because of primary or...
secondary loss of efficacy, which affected drug survival.\textsuperscript{11}

There has been no research in India that examined the details of switching in biologic administration to psoriatic patients and the reasons for switching between multiple biologics. To the best of our knowledge, our study on biologics switching is the first of its kind in the Indian scenario.

**METHODS**

**Patients**

Our study on biologics switching is a retrospective cohort study. It was conducted in patients who were diagnosed with psoriasis vulgaris clinically and treated with biologics between January 2016 and December 2019 in the Department of Dermatology, Madras Medical College and Rajiv Gandhi Government General Hospital. Only those who were observed for more than 52 weeks were enrolled in this study. The details of the patient, treatment and follow up were extracted from the respective biologic registers. Forty-four patients were treated with biologics in the above period. Of these, two patients were lost to follow up and the remaining forty-two patients’ details were taken for study. The sample size is 42.

**Clinical factors**

Age of the patient, initial psoriasis area and severity index (PASI) score, smoking habit and body mass index (BMI) were compared between non-switched and switched groups.

**Treatments**

Three biologic agents - Infliximab (IFX), Etanercept (ETN) and Secukinumab (SEC) - were available for treating moderate to severe psoriasis at our department of Dermatology, Madras Medical College and Rajiv Gandhi Government General Hospital since 2014. Since the Biologics administered were completely government-funded, we had issues of non-availability of biologics occasionally.

IFX was administered intravenously (5 mg/kg) at weeks 0, 2 and 6 weeks. ETN was administered subcutaneously as 50 mg pre-filled injections weekly for 24 weeks. SEC was administered as 300 mg subcutaneous injections at weeks 0, 1, 2, 3, 4 followed by 300 mg every 4 weeks for 4 months. Each 300 mg is given as 2 s.c injection of 150 mg.

**Efficacy assessment**

Psoriasis area and severity index were measured at the first biologic treatment (week 0) and weeks 14-16, and at the same time points in patients who were switched to a second biologic.

**Reasons for alterations in biologic treatment**

Reasons for changing treatment regimen were categorized as follows: inefficacy, including primary failure (not achieving a ≥50% PASI score improvement at 24 weeks) and secondary failure (losing initial efficacy). However, relapse occurred within a short period after treatment, though they responded initially; AE, including infusion reaction. Non-availability of biologics (since the biologics used are completely government-funded). The reason for biologic switching and the second biologic to which the patient had been switched were noted.

When a patient shows inefficacy, encountered AE or when the biologics had availability issues, the decision to switch to an alternative biologic was made. Since this was a retrospective study, switching of biologics is not always dependent on an objective index such as psoriasis area severity index or dermatology life quality index, but rather it is dependent on the patient’s request or physician’s decision.

**Data entry and statistical analysis**

The data related to patient’s age, gender, PASI score, biologics and reason for switching were entered in google sheets. Statistical analysis was conducted with SPSS Statistics 24.0 (IBM corporation, Armonk, NY).

**RESULTS**

**Patients**

Forty-four patients were initiated treatment with biologics between January 2016 and December 2019 in the Department of Dermatology, Madras Medical College and Rajiv Gandhi Government General Hospital. Of these, 2 patients were excluded as they were lost to follow up, and 42 cases were enrolled in this study. The minimum follow-up period was 52 weeks. The overall mean age was 43.9 (±13.7); 69% were males and 21% were smokers. The mean PASI score at baseline was 27.1 (±12.1). First-line therapies were IFX (n=10), ETN (n=21) and SEC (n=11). A total of 19 patients (45%) subsequently required switching to another biologic. The number of patients switched in IFX, ETN and SEC subgroup were 3 (30%), 11 (52%) and 5 (45%) respectively (Table 1).

**Reasons for switching to a different biologic**

The major reason for switching was inefficacy due to secondary failure (n=10; 53%). The total number of patients switched due to the non-availability of biologics and AE was 8 (42%) and 1 (5%) respectively (Table 2). The adverse event that occurred with IFX is infusion reaction. There were no switches due to the development of infection.
Table 1: Demographic characteristics of the study population.

| Demographic characteristics | First treatment | Total |
|----------------------------|----------------|-------|
|                            | Infliximab | Etanercept | Secukinumab | |
| No. of patients            | 10         | 21        | 11          | 42 |
| Mean age±SD in years       | 46.8±12.6  | 42.7±13.7 | 43.7±13.6   | 43.9±13.7 |
| Men, N (%)                 | 9 (90)     | 10 (47)   | 10 (90)     | 29 (69) |
| Smokers, N (%)             | 2 (20)     | 1 (5)     | 6 (54)      | 9 (21) |
| Mean BMI±SD, kg/m²         | 21.4±3.8   | 23.4±3.5  | 23.7±3.8    | 23.0±3.8 |
| PASI baseline (mean±SD)    | 28.2±13.6  | 26.4±10.2 | 27.3±14.4  | 27.1±12.1 |
| No. of switched patients, N (%) | 3 (30) | 11 (52) | 5 (45) | 19 (45) |

Table 2: Reasons for switching to different biologics.

| Variables                              | Infliximab | Etanercept | Secukinumab | Total |
|----------------------------------------|------------|------------|-------------|-------|
| No. of patients                        | 3 (100)    | 11 (100)   | 5 (100)     | 19 (100) |
| Inefficacy due to primary failure      | -          | -          | -           | -     |
| Inefficacy due to secondary failure    | 1 (33)     | 8 (73)     | 1 (20)      | 10 (53) |
| Adverse event                          | 1 (33)     | -          | -           | 1 (5)  |
| Non-availability                       | 1 (33)     | 3 (27)     | 4 (80)      | 8 (42) |

Table 3: Demographic characteristics of continuously treated and switched cases.

| First biologic | No. of patients | Mean age±SD | Male, N (%) | PASI baseline (mean±SD) | Smokers, N (%) | Mean BMI ±SD, kg/m² | PASI baseline (mean±SD) | Smokers, N (%) | Mean BMI ±SD, kg/m² |
|----------------|----------------|-------------|-------------|-------------------------|----------------|---------------------|------------------------|----------------|---------------------|
| Infliximab     | 7              | 46.7±11.4   | 7 (100)     | 28.1±13.5               | 3 (42.9)       | 21.2±4.0            | 10 (100)               | 2 (66)         | 21.7±3.8            |
| Etanercept     | 10             | 43.4±11.0   | 6 (60)      | 26.1±10.0               | 0 (0)          | 24.0±3.1            | 1 (9)                  | 4 (36)         | 22.8±3.8            |
| Secukinumab    | 6              | 41.2±12.2   | 6 (100)     | 21.5±5.3                | 3 (50)         | 23.9±3.8            | 3 (60)                 | 4 (80)         | 23.5±4.0            |
| Total          | 23             | 45.4±11.0   | 19 (83)     | 25.5±9.8                | 6 (26)         | 23.2±3.8            | 19 (83)                | 10 (53)        | 22.8±3.7            |

BMI, body mass index; PASI, psoriasis area and severity index; SD, standard deviation; y, years.
Table 4: Average duration for relapse (period of remission) after stopping biologic.

| Biologics                  | Average duration for relapse (period of remission) after stopping the Biologic |
|----------------------------|--------------------------------------------------------------------------------|
| Infliximab: mean duration±SD, months | 6±2.1                                                                         |
| Etanercept: mean duration±SD, months   | 3.4±2.1                                                                       |
| Secukinumab: mean duration±SD, months  | 2±1.7                                                                         |

SD, standard deviation.

Table 5: Recommendations for switching therapy to treat moderate-to-severe psoriasis.

| Switching from conventional systemic therapy to biologic therapy | General considerations                                                                                     |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
|                                                                    | When switching for safety reasons, a washout period is recommended until the safety parameter is normalized or stabilized |
|                                                                    | When switching due to lack of efficacy, direct transition, or an overlap period can be considered         |
|                                                                    | Use approved induction doses when starting biologic therapy                                             |
| Switching from acitretin                                          | Can be performed without a washout period                                                                |
|                                                                    | Women of childbearing age should continue with contraception for 2 years, as recommended for the use of acitretin |
| Switching from cyclosporine                                       | Can be performed without a washout period                                                               |
|                                                                    | A short overlap period with biologic therapy (e.g., 2–8 weeks) can be considered to reduce the risk of rebound in partial responders; taper the dose of cyclosporine as soon as possible |
| Switching from methotrexate                                       | Can be performed without a washout period                                                               |
|                                                                    | Methotrexate can be overlapped or used concomitantly with approved biologics                            |
| Switching from one biologic to another                            | General considerations                                                                                   |
|                                                                    | After considering dosage adjustments, switching should be performed if patients have an inadequate response (i.e., not achieving at least PASI 50) at the end of the induction phase (primary non-responders) or if efficacy is lost over time (secondary non-responders) |
|                                                                    | When switching for safety reasons, a washout period is recommended until the safety parameter is normalized or stabilized |
|                                                                    | When switching due to lack of efficacy, no washout period is necessary; switch to the new biologic at the time of the next scheduled dose of the original therapy |
|                                                                    | Start the new biologic with the approved induction dosing, followed by maintenance dosing                |

| Switching from infliximab                                        | Initiation of the first treatment with adalimumab, etanercept, or ustekinumab after a treatment transitioning from infliximab can be considered as early as 2–4 weeks after the last infliximab dose, particularly in cases of treatment failure |
| Switching from etanercept                                         | Administer the first treatment with adalimumab, infliximab, or ustekinumab after a treatment transitioning from etanercept at the time point of the next scheduled dose (typically 1 week) |
| Switching from adalimumab                                         | Administer the first treatment with etanercept, infliximab, or ustekinumab after a treatment transitioning from adalimumab at the time point of the next scheduled dose (typically 2 weeks) |
| Switching from ustekinumab                                        | Initiation of the first treatment with adalimumab, etanercept, or infliximab after a treatment transitioning from ustekinumab should be performed at 8–12 weeks but can be considered as early as 2–4 weeks after the initial biologic dose in cases of treatment failure |

PASI, psoriasis area and severity index.

The characteristics of patients experiencing inefficacy or AE with IFX, ETN and SEC are shown in (Table 3). The average duration for relapse (period of remission) after stopping biologic is given in (Table 4). IFX was found to have the highest remission period (6 months ±2.1) when compared with ETN and SEC.

DISCUSSION

Psoriasis is a chronic relapsing disease, seen as a papulo squamous disorder, affects approximately 1-3% of the general population. It is being increasingly recognized that psoriasis is a systemic disease and not merely confined to the skin alone. Metabolic syndrome is also being increasingly associated with the disease. Various therapeutic approaches are already in use for the disease. Most conventional modalities of therapy have end-organ damage and are toxic in the long term. Therefore, one has to use the drugs with caution, keeping in mind the disability caused by the disease in a working individual in India, which is a resource-poor country. The invention of biologics has made the treatment of psoriasis revolutionary.
Biological therapy became available for psoriasis in the last two decades. Biologic therapies for psoriasis utilize molecules that are designed to block specific molecular steps important in the pathogenesis of psoriasis and now comprise a number of well-established, licensed treatment options for patients with severe disease. There are several biologic drugs in use in India for various indications, both dermatologic and non-dermatologic. However, there are no existing guidelines in India as of now regarding the use of biologics.

Alefacept was the first biological agent approved by the US food and drug administration for the treatment of moderate-to-severe chronic plaque psoriasis in 2003. Though it has been discontinued in 2011, several other biologics came into clinical use and are highly effective. Among tumor necrosis factor (TNF)-alpha blockers, etanercept was the first biologic to be introduced in the year 2000 and its approval for psoriasis was obtained in 2004; infliximab in 2002.12,13 Adalimumab in 2008, golimumab for PsA in 2009, and certolizumab pegol was approved in 2018 for the treatment of psoriasis.14,15 Ustekinumab, an interleukin IL-12, and IL-23 p40 subunit blocker, was approved for psoriasis in 2009.16 IL-17 blockers, for example, secukinumab, were approved in 2015 for psoriasis in adult patients, and ixekizumab in 2016 while brodalumab, IL 17 receptor A blocker, was approved in the year 2017.17 Itolizumab, an Indian biologic which acted upstream by blocking the co-stimulation between CD6 and activated leukocyte-cell adhesion molecule (ALCAM), was approved in 2013 for psoriasis.18 IL-23 P19 subunit blockers are newer biologics, with tildrakizumab being approved in 2018, guselkumab in 2017, and risankizumab in 2019.19,21

Biologics commonly used in psoriasis are classified into four classes according to their target molecules: inhibition against tumor necrosis factor (TNF)-α, Interleukin (IL)-12/23p40, IL-17A or IL-17 receptor A. Each drug has its own characteristic efficacy, indications, and side-effects. Based on these characteristics, dermatologists select brands for suitable patients.

Treatment with biologics is now standard treatment for moderate to severe cases of psoriasis due to the high efficacy and promising safety profile. Efficacy is particularly notable in patients who do not respond to conventional treatments, such as retinoids, cyclosporine or phototherapy. Further, biologics are extremely effective in treating cases with nail, scalp and joint involvement, which often fail to improve with conventional treatments.

However, in practice, there are some patients in whom biologics show little efficacy from the beginning, or in whom they lose their efficacy after successful induction for a certain period. Additionally, the efficacy is sometimes weakened or may present with new adverse effects when the original drug is re-administered after a certain period during which administration of the medication is stopped. In such cases, administration of the original biologic may be terminated, or the patient may be switched to another biologic. Thus, the total value of a drug is judged by factors such as efficacy, safety, usefulness, and economic burden.

The biologics available in our setup for the treatment of psoriasis were Infliximab (IFX), Etanercept (ETN), Secukinumab (SEC). Hence the results of our study were confined to these three biologics. The main findings of this study are that the necessity to switch to the second biologic is found to be least with Infliximab (n=3, 30%), however, it had an adverse reaction. The most common reason for the biologic switch is ineffectiveness (n=10; 45%)

Based on the study on biologic switching by Honda et al, patients who switched to a different biologic exhibited a substantial reduction in PASI score after switching. This result suggests that switching to a different biologic may indeed improve psoriasis in patients who do not sufficiently respond to the first treatment. Their study highlights the presence of refractory cases who required biologic switch even after dose escalation and in general, patients who experienced secondary failure achieved better responses than patients with primary failure. The results of our study are similar to that of findings by Honda et al.

In our study, IFX is associated with infusion reactions and secondary failure. Although infliximab is generally well tolerated, there are some adverse effects associated with its use. Adverse events are a major reason for discontinuation of infliximab therapy in patients with psoriasis. A Canadian multicenter retrospective study showed that 15% of patients withdrew from infliximab therapy owing to adverse effects.22 Infusion reactions occur in about 3-22% of patients of psoriasis treated with infliximab.23 Infusion reactions can be classified as acute or delayed, depending on the time of onset, and as mild, moderate, or severe, depending on the severity of the symptoms.24,25 Most of these reactions are mild or moderate and only a few are severe. Infusion reactions occurring during and within 24 hours of infusion are categorized as acute infusion reactions, and the symptoms include headache, flushing, hypotension/hypertension, dizziness, shortness of breath, nausea, sweating, rise in temperature, and other symptoms of anaphylaxis, such as urticaria and rash.26 Delayed infusion reactions occur between 24 hours and 14 days after an infusion and are generally characterized by myalgia, arthralgia, fever, urticarial rash, and malaise.27 Although the exact mechanism of infusion reactions is not known, the development of antibodies to infliximab (ATIs) may play a significant role. The presence of ATIs is associated with an increased incidence of infusion reactions.28 We have encountered one case with acute infusion reaction to Infliximab. The patient developed urticaria and hypotension during infusion.
Piaserico et al studied the efficacy of switching between TNF-alpha inhibitor. According to them, in 105 patients who switched to a second TNF-alpha inhibitor who had complete follow-up data, 75% improvement in the Psoriasis area severity index score (PASI 75) was reached by 29% after 16 weeks and by 45.6% after 24 weeks. Patients who switched because of secondary loss of efficacy (loss of initial PASI 75 response) or adverse events/intolerance were more likely to reach PASI 75 than those who switched as a result of primary inefficacy (PASI 75 never achieved) (hazard ratio 2.7; 95% confidence interval 1.3-5.5 vs hazard ratio 2.0, 95% confidence interval 1.0-3.9 and 1, respectively). Paul S et al conducted a systematic review of fifteen studies to know the efficacy of anti-tumor necrosis factor (TNF) therapy in patients with psoriasis previously treated with a different anti-TNF agent. They also concluded that Although response rates to a second TNF antagonist were lower than for a first, a substantial proportion of patients in every study achieved treatment success.

Gottlieb et al studied the efficacy and safety of infliximab in patients with plaque psoriasis who had an inadequate response to etanercept. According to them, at week 10, 65.4% of patients (138 of 211; 95% confidence interval 58.6%-71.8%) achieved a PGA score of clear (0) or minimal (1) (primary end point). This response was durable through week 26, at which time 61.3% (122 of 199; 95% confidence interval 54.2%-68.1%) achieved a PGA score of clear (0) or minimal (1). There were no unexpected side effects or safety concerns. They concluded that after switching to infliximab, a substantial proportion of patients with psoriasis and inadequate response to etanercept experienced rapid and durable improvement. We also encountered similar results when switched from etanercept to infliximab.

Sator et al studied the efficacy and safety of adalimumab in patients with plaque psoriasis who previously received another biologic agent. They concluded that adalimumab therapy in patients with plaque psoriasis previously treated with other biologic agents demonstrates effectiveness, safety, and improvement in the quality of life. In contradictory, Bhutani reported the paradoxical worsening of psoriasis when switching from etanercept to adalimumab. They also concluded that, despite the well-known average efficacy advantage of adalimumab over etanercept, some psoriasis patients experience better clinical outcome with etanercept than adalimumab.

Chiricozzi et al conducted a retrospective observational multicenter study aimed to describe the efficacy and safety of ustekinumab in secukinumab non-responder patients and concluded that ustekinumab was safe and effective in treating patients unresponsive to secukinumab. Georgakopoulos et al conducted a 12 weeks retrospective multicentre study on biologic switching between interleukin 17A antagonists secukinumab and ixekizumab. They arrived at the following results: a proportionally high number of patients with prior exposure to secukinumab will achieve efficacious outcomes following 12 weeks of ixekizumab treatment, safety outcomes with secukinumab do not correlate with ixekizumab safety outcomes and patients with prior extended exposure to secukinumab may be favourable candidates for ixekizumab therapy. Sherman et al studied the efficacy of ixekizumab following secukinumab failure and found that patients with moderate-to-severe psoriasis seem to be amenable to treatment with ixekizumab following secukinumab failure.

Limited guidance is available on how and when to switch therapies to achieve optimal clinical outcomes in real-world clinical practice. Perhaps the best guidance to date has been provided by the Transitioning Therapies program, which developed a consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis based on systematic literature reviews and expert opinions of 107 dermatologists from 33 countries (Table 5). The body of evidence on switching therapies in psoriasis indicates that individuals respond differently to the different biologics approved for treating moderate-to-severe psoriasis, even when the biologics share a mechanism of action targeting TNF-alpha. Thus, failure on one agent does not predict future treatment failure with different agents, and prompt alteration of treatment should be a priority for patients who are failing to meet their goals given the wide range of therapies already available and in late-stage clinical development for the management of moderate-to-severe psoriasis.

The availability of multiple biologic therapies with different mechanisms of action will expand the options for switching therapy after the failure of an initial biologic. As these new therapies become available, patients’ views about their disease are changing and, therefore, better outcomes such as almost complete clearance may be achievable by a substantial proportion of patients.

There were some limitations to this study. This was a survey of a single institute and there were a relatively small number of patients. This was a retrospective study and switching of biologics is not always dependent on an objective index such as psoriasis area severity index or dermatology life quality index, but rather it is dependent on the patient’s request or physician’s decision.

A larger multicenter study is needed to determine the optimal treatment for psoriasis and psoriatic arthritis patients. In the future, more drugs will be introduced into the market. The usefulness of all drugs needs to be evaluated through detailed observation on a larger scale.
CONCLUSION

The results from this study show that infliximab had the least tendency to switch to the second biologic, however, it had adverse reactions and the primary cause for switching was inefficacy. To the best of our knowledge, our study on biologics switching is the first of its kind in the Indian scenario.

In the past, it was generally accepted that treatment would help manage psoriasis signs and symptoms but that, for most patients, complete clearance was not attainable and some skin lesions would always be present. However, patients are now expecting safe and complete clearance and good tolerability, and are dissatisfied with anything less, especially when they may have experienced complete clearance with pharmacologic treatment in the past. With the evolving landscape of safe and effective biologic agents for the treatment of moderate-to-severe psoriasis, such high expectations are likely to be attainable for many patients. Therefore, an essential component to maximizing treatment success is communication between patients and practitioners to develop realistic treatment goals that, if achieved, will satisfy the patient and improve his or her quality of life.

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