

Treatment of psoriasis with biologic agents in Malta

Liam Mercieca, Michael J. Boffa, Eileen Clark, Lawrence Scerri, Susan Aquilina

Abstract

Introduction: Biologic therapy has revolutionised the treatment of moderate to severe psoriasis leading to improved clinical outcomes and quality of life scores. This study aims to determine current biologic use in psoriatic patients at our Dermatology department at Sir Paul Boffa hospital, Malta.

Method: All patients who were administered biologic therapy for psoriasis in Malta until the end of 2014 were included. Data included demographic details, disease duration and severity, biologic use and duration, previously attempted treatments, side effects, early and late response to biologic using Psoriasis Area Severity Index (PASI) scores and Dermatology Life Quality index (DLQI) scores.

Results: A total of 36 patients were started on a biologic between 2009 and 2014 for psoriasis (M:25, F:11) with a mean age of 46.9 years. These included etanercept ($n=22$), infliximab ($n=8$), adalimumab ($n=4$) and ustekinumab ($n=2$). Secondary failure was the main reason why biologics were stopped and switched. Most patients had an improvement in their PASI scores after 2 to 4 weeks of starting the biologic and had a PASI 90 score improvement. All patients had more than a 5 point improvement in DLQI score.

Discussion: Biologic use in our department is on the increase. Our patients had considerable improvements in their PASI and DLQI scores. Secondary failures have occurred usually after 2 to 4 years and switching has yielded positive results. Biologics are expensive drugs and recently we have switched to cheaper biosimilars. Doctors should be aware of the treatment options available for psoriasis patients, their possible side effects and when to refer to our department. In most cases a satisfactory response can be achieved.

Keywords:

psoriasis, biologics, Malta

Introduction

Treatment of psoriasis has improved dramatically over the past few years with new options becoming readily available. First line treatment includes topical therapy followed by ultraviolet (UV) therapy, with acitretin and the oral immunomodulators methotrexate and ciclosporin, as second line interventions.¹ Biologics have revolutionised the management of severe psoriasis offering improved clinical outcomes and quality of life scores. They target specific immune pathways in the pathophysiology of psoriasis. These are expensive drugs, with typical drug cost ranging from 10,000€ to 18,000€ per patient per year.²

Current local guidelines (based on European and UK guidelines) recommend four biological

Liam Mercieca MD, MRCP (Edin.)*
Higher Specialist Trainee in Dermatology,
Sir Paul Boffa Hospital
liam.mercieca@gov.mt.

Michael J. Boffa MD, FRCP (Lond.), MSc (Lond.)
Consultant Dermatologist,
Sir Paul Boffa Hospital

Eileen Clark MD, MRCP (UK), MRCP (Dermatology)
Consultant Dermatologist,
Sir Paul Boffa Hospital

Lawrence Scerri MD, FRCP (Lond.), FRCP (Glasg.)
Consultant Dermatologist
Chairman,
Department of Dermatology and Venereology,
Sir Paul Boffa Hospital

Susan Aquilina MD, FRCP (UK)
Consultant Dermatologist,
Sir Paul Boffa Hospital

*Corresponding Author

agents in psoriasis. These are indicated in patients with moderate to severe psoriasis who have failed or are intolerant of other treatment options. These include infliximab, etanercept, adalimumab and ustekinumab.^{1,3} Secukinumab and the cheaper biosimilars of infliximab have also been recently

approved for use in psoriasis.⁴ New biologic agents are constantly being developed targeting different immune pathways (Table 1). A cheaper biosimilar of adalimumab is expected to be available in 2018 when the European patent of the originator drug (Humira[®]) expires.

Table 1: Biologics approved in psoriasis, year of FDA approval, mode of action and other approved indications (until date of submission)

Biologics for Psoriasis (Year of FDA approval)	Mode of Action, Dose and Administration	Other Approved Indications
1. Etanercept (Enbrel [®]) (2004); adults and children >6yrs	TNF alpha blocker; 50mg (0.8mg/kg) s.c. once a week	Rheumatoid arthritis, Psoriatic arthritis, Juvenile Idiopathic Arthritis, Ankylosing spondylitis
2. Infliximab (Remicade [®]) (2006) Remsima [™] (EMA approved 2013) Inflectra [™] (EMA approved 2013)	TNF alpha blocker; 5mg/kg i.v. infusion at weeks 0, 2, 6 and then every 8 weeks	Rheumatoid Arthritis, Ankylosing spondylitis, Psoriatic arthritis, Inflammatory Bowel Disease
3. Adalimumab (Humira [®]) (2008)	TNF alpha blocker; 80mg s.c., followed by 40mg every 2 weeks	Rheumatoid arthritis, Juvenile Idiopathic Arthritis, Psoriatic arthritis, Ankylosing spondylitis, Inflammatory Bowel Disease
4. Ustekinumab (Stelara [®]) (2009)	Interleukin 12 & 23 blocker; 45mg (90mg if >100kg) s.c., repeated after 4 weeks, and then every 12 weeks	Psoriatic arthritis
5. Secukinumab (Cosentyx [®]) (2015)	Interleukin 17A blocker; 300mg s.c. at weeks 0, 1, 2, and 3 and then every 4 weeks	Nil

Since biologics are expensive drugs, cost effectiveness is an important factor to consider in the commencement and availability of these drugs. Clear evidence-based eligibility criteria are important to target the appropriate psoriatic population.

The Psoriasis Area Severity Index (PASI) score is used to assess disease severity and response to treatment in psoriasis. A PASI score of ≥ 10 (range 0–72) has been shown to correlate with a number of indicators commonly associated with severe disease such as need for hospital admission or use of systemic therapy.¹ Satisfactory response is usually considered to be a 75%, or even better, a 90% improvement as compared to baseline score. This is reported as PASI 75 and PASI 90 respectively. The Dermatology Life Quality index (DLQI) score is a validated tool to assess the impact of skin diseases ranging from 0 to 30, with scores more than 10 indicating a significant impact on quality of life.

Biologic use in Malta started in 2009 and this

study gives an overview of the patient characteristics and clinical outcomes to date.

Aim

A cross sectional study to determine current biologic use in psoriasis: a local perspective.

Method

All patients who were administered biologic therapy for psoriasis in Malta until the end of 2014 were included in the study. Patients who were started on a biologic for psoriatic arthritis by the rheumatologists were excluded. Data collected included gender, age, nationality, biologic used, date of commencement, concomitant medications, disease duration prior to biologic, associated comorbidities, previously attempted treatments, reason for stopping previous treatments, investigations before starting a biologic, early and late response to biologic using PASI and DLQI scores and side effects reported.

Results

There were a total of 36 psoriasis patients who were started on a biologic between 2009 and 2014 (N=36); 25 of the patients were male, 11 were female. They were all patients with stable chronic plaque psoriasis and none had the erythrodermic or pustular forms. Twenty-two of these patients were on etanercept, 8 patients were on infliximab, 4 patients were on adalimumab and 2 patients were on ustekinumab. The biologic was indefinitely discontinued in 12 out of these 36 patients. Reasons for discontinuation included patients going abroad indefinitely, death from other causes, non-compliance, patient refusal and worsening of heart failure post myocardial infarction. In 2014, there were 24 patients who were on biologics for psoriasis: 14 were on etanercept, 6 were on infliximab and 4 on adalimumab.

The ages of the 36 patients ranged from 19 to 70 years, with a mean age of 46.9 years and a median of 46 years. Twenty-nine of the patients were Maltese, two were Canadian, three patients were from the UK and two patients were Italian. The patients were on a variety of concomitant medications with methotrexate being the commonest ($n=14$). Disease duration prior to biologic therapy ranged from 2 to 55 years, with a mean of 16.7 years and a median of 14 years. Six of the patients had psoriatic arthritis as a later comorbidity, but were started on a biologic by a dermatologist.

Psoriatic treatments attempted before the current biologic included: phototherapy [narrow band UVB (28) or psoralen UVA (4)], methotrexate (29), acitretin (16), ciclosporin (15), etanercept (4), infliximab (2) and ustekinumab (2). The reason for stopping these medications included: inadequate control (24) and side-effects from methotrexate (6), ciclosporin (5) and acitretin (4). Secondary failure was the main reason why biologics were stopped and switched.

All patients had routine bloods, hepatitis screen, tuberculosis screen (Mantoux or Quantiferon and Chest X-ray) taken, according to protocol. HIV testing is done in high risk patients and ANA testing is carried out if indicated. Patients on infliximab are seen every two months in the dermatology ward whilst the patients on other biologics are usually seen according to response and according to whether they are on concomitant methotrexate. Quantiferon test is not done annually

and none of the patients had latent TB.

Most patients had an improvement in their PASI scores after 2 to 4 weeks of starting the biologic. Currently, of the 14 patients on etanercept, 57% ($n=8$) achieved a PASI 90, 29% ($n=4$) have a PASI 75 and 14% ($n=2$) had secondary failure after 2 years. Of the 8 patients on Infliximab, 63% ($n=5$) had a PASI 90, 25% ($n=2$) had a PASI 75 and 13% ($n=1$) had secondary failure after 1 year. There were 4 patients started on adalimumab in 2014; 3 of them achieved a PASI 90 and 1 patient achieved a PASI 75. All our patients had more than a 5 point improvement in DLQI score. Facial and periorbital swelling, lethargy and a chest infection were reported as possible side effects with etanercept. No side effects were reported for infliximab, adalimumab and ustekinumab. Injection site or infusion reactions, reactivation of tuberculosis, severe infections and sepsis were never reported as side effects for any biologic used.

Discussion

Biologic use in our department is on the increase but is heavily determined by the treatment options listed on the national health formulary and available resources.

Biologic use for psoriasis in Malta started in 2009, with etanercept being the first biologic available, followed by infliximab in 2011 and later adalimumab in 2014. Etanercept stopped being available for new psoriasis applications in 2013, but patients doing well on etanercept continued to receive it. Ustekinumab was never available on the national health system - the two patients on ustekinumab in this study had the drug provided for them through private arrangements which were subsequently withdrawn. In our study, patients on biologics were predominantly male (69% male, 31% female), suggesting that men are at a higher risk for severe psoriasis. This is also the situation in other countries.⁵⁻⁶

This study shows that our department is following the latest guidelines. Our patients are first treated with topical therapy, then phototherapy or second line agents including methotrexate, acitretin and ciclosporin. If these fail, are contraindicated or cause intolerable side effects, a biologic is started. It is interesting to note that most patients had an adequate ($\geq 75\%$ decrease in PASI score) and sometimes impressive response initially to the biologic, with most patients achieving complete or

almost complete clearance of their psoriasis. There were a few patients whose psoriasis started to relapse (described as secondary failure) after 2 to 4 years of successful treatment with the biologic, that necessitated switching to another biologic to maintain control of the psoriasis. Switching between biologics that act on the TNF alpha pathway, such as etanercept to infliximab or adalimumab, and infliximab to adalimumab or etanercept, has yielded positive results in these few cases in our department.

There is evidence that concomitant treatment with methotrexate might increase biologic efficacy by reducing the antigenicity towards biologics and their clearance.⁷⁻⁸ Sixty-one percent of our patients on biologics are on concomitant methotrexate therapy, usually at low dose (often 7.5 mg per week). In our experience there were never any serious side effects reported and this combination has been working well.

In 2015, patients who were started on a biologic in the previous years will be kept on the same treatment whilst new patients will be started on the cheaper biosimilar of infliximab (Remsima™) as determined by our national health system. This should result in a 30 percent decrease in the total cost of biologic therapy per patient per year. Future considerations to increase cost-effectiveness of psoriasis treatments include the provision of psychological support in this often stress-related condition and nursing support with topical medications, especially in the elderly. It is

also important to follow up patients regularly so that treatment failures can be identified early and treatment changed accordingly. Testing of drug and antibody levels will probably play an important role in optimizing treatment in the near future.⁹⁻¹⁰ For example, it has been estimated that one-third of patients on standard doses of adalimumab have drug levels higher than the therapeutic range.¹¹

In the case of severe side-effects with Remsima™, or if primary or secondary failure develops to it, an application to the Exceptional Medicinal Treatment Committee (Directorate for Pharmaceutical Affairs) would need to be made to allow switching to another biologic. This could be to another TNF alpha blocker (Adalimumab or Etanercept) or to a biologic acting on a different immune pathway (Ustekinumab or Secukinumab). A limitation to the availability of all of these biologics on the National Formulary is, of course, their high cost.

Conclusion

Psoriasis is a chronic condition that can have a significantly negative impact on quality of life. Our patients had considerable improvements in their PASI and DLQI scores with biologic treatment. It is important that primary care doctors are aware of the treatment options available for patients with psoriasis, their possible side effects and when to refer patients to our department. In most cases a satisfactory response can be achieved.

Figure 1: Patient with psoriasis before biologic treatment



Figure 2: Patient clear from psoriasis 6 months after commencing biologic treatment with Ustekinumab



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