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REVIEW ARTICLE

Experience and challenges for biologic use in the treatment of moderate-to-severe psoriasis in Africa and the Middle East region

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ABSTRACT

The incidence of psoriasis in Africa and the Middle East (AfME) is high as in other regions and represents a significant problem for both dermatologists and patients. Psoriasis co-morbidities such as obesity, cardiovascular disease and psoriatic arthritis (PsA) are also particularly common in these regions and may be under-recognized and under-treated. Despite this, regional guidelines to aid physicians on the appropriate use of biologic agents in their clinical practice are limited. A group of expert dermatologists from across the AfME region were surveyed to help establish best practice across the region, alongside supporting data from the literature. Although biologics have significantly improved patient outcomes since their introduction, the results of this survey identified several unmet needs, including the lack of consensus regarding their use in clinical practice. Discrepancy also exists among AfME physicians concerning the clinical relevance of immunogenicity to biologics, despite increasing data across inflammatory diseases. Significant treatment and management of challenges for psoriasis patients remain, and a move towards individualized, tailored care may help to address these issues. The development of specific local guidelines for the treatment of both psoriasis and PsA could also be a step towards understanding the distinct patient profiles in these regions.

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Introduction

Biologic agents have been available in Africa and the Middle East for the treatment of moderate-to-severe psoriasis for over a decade; however, regional guidelines to guide local physicians on the appropriate use of these agents in their clinical practice are limited. The burden of psoriasis in Africa and the Middle East is high as in other regions of the world (1,2), and may in fact be higher, with a prevalence of almost 10% recorded in Indian ethnicity in a Johannesburg study (3) compared to 1–3% in Western Caucasian populations (4–6). A study in Iran found 55% of psoriasis patients had facial involvement – an indicator of more severe disease (7). These differences reflect genetic differences between populations.

In the region, currently only South Africa and Saudi Arabia have national guidelines (8,9). This is a concern for several reasons. Firstly, psoriasis co-morbidities such as metabolic syndrome, obesity, cardiovascular disease and PsA are particularly common in African and Middle Eastern patients (10) and may be under-recognized and under-treated. Secondly, infections such as tuberculosis (TB) and hepatitis are endemic in certain parts of the region (11,12) and require special consideration with respect to the use of biologic agents.

With few published standards of care or a consensus on how to approach psoriasis patients, there are still significant unmet needs, despite the publication of a review on the management of psoriasis in Africa and the Middle East in 2011 (13). In order to address this situation, an expert group met to discuss key issues relating to the treatment of psoriasis patients across Africa and the Middle East. In addition, an online survey to establish expert views and practice from across the region was conducted. The survey questions were centered on physician experience with biologics in clinical practice, and the assessment and screening of patients. The results of this survey are presented here. A literature search was performed in order to identify new data that may help inform and influence clinical practice. The PubMed database was searched for papers published since 01 January 2009 in order to collate clinical data and guidelines published since the introduction of biologics in the region. Searches were limited to 'Adult: 19 + years' and 'Humans' and key search terms used were "Psoriasis" OR ("Psoriasis" AND ("Biologics" OR "Adalimumab" OR "Etanercept" OR "Infliximab" OR "Ustekinumab")). Relevance to the topic was determined by scanning the titles, and where available the abstracts, of retrieved articles. Relevant data on the key topics addressed are summarized below.

Treatment of moderate-to-severe psoriasis in Africa and the Middle East

As the previous review of management in the region noted, the diagnosis of psoriasis is not a challenge for an experienced dermatologist (13), and there are many validated instruments used to assess disease severity and quantify the impact of disease on a patient. According to our survey, dermatologists in the Middle East routinely use a variety of screening tools and assessment measures to help diagnose and assess disease, and to identify co-morbidities. PASI (psoriasis area severity index) is cited as the most

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frequently used tool for scoring disease severity, although DLQI (dermatology life quality index) and BSA (body surface area) are also frequently mentioned. Specific tools have also been developed – such as the Moroccan Arabic form of the DLQI, which has been shown to be reliable in clinical practice (14). However, despite the availability of accurate tools to assess disease severity, the use of biologic therapies remains low worldwide, possibly indicating that eligible patients are being under-treated (15). In a European survey of dermatological practices in Germany, only 31% of patients with moderate-to-severe psoriasis were receiving a systemic therapy (16,17). Experience of TNF-inhibitor prescribing rates among our expert group ranged from regular prescribing at every clinic, to only once every 2 months. It can be assumed that experience is likely to be lower among general practicing dermatologists. Reasons cited by dermatology colleagues' not using biologics more widely included unfamiliarity, cost and compliance of patients. Despite the relatively low uptake compared with Europe, the consensus is that biologic therapies have made a substantial impact on clinical practice since their introduction. The physicians surveyed suggested that the most noticeable benefits have come in terms of patients' quality of life, as supported by the number of patients attending follow-up clinics for retreatment. The criteria most frequently used in deciding which biologic to prescribe for a given patient are the likelihood of early response, the predicted long-term response, and the available safety data. Such decisions, however, may be made without access to specific local data and information. Up-to-date national guidelines and recommendations for the treatment of moderate-to-severe psoriasis exist in Saudi Arabia and South Africa (8,9) but the majority of dermatologists follow either the European (18) or American (19) guidelines, or a mix of both. While these offer a framework for clinical practice, they do not cover local medical, legal, religious or practical considerations or offer guidance for challenging cases.

Overall, the survey responses suggest that despite positive patient outcomes since the introduction of biologic agents for the treatment of moderate-to-severe psoriasis in Africa and the Middle East, many eligible patients are still not receiving biologic therapies, and there is no real consensus regarding their use in clinical practice.

New trial data to support clinical decision making

Even among our expert group surveyed, there are mixed opinions with regard to the importance of clinical trial data, with some believing that trial data should guide local policy and practice, and others indicating that registries and real-world data are more relevant . As a group, all of the experts believed that clinical trial results could generally be applicable to clinical practice, even from studies in different patient populations. There are few studies examining the efficacy of combining topical agents with biologic therapy, despite this strategy being used frequently in "real-world" practice. In the recently published REFINE study, patients who were reduced to the maintenance dose of etanercept (50 mg once weekly) were able to maintain their clinical response with the addition of topical therapies if required, with no notable differences in PASI responses compared to those who stayed on the initial label dose of 50 mg twice weekly (20). The opportunity to use a topical agent with etanercept maintenance dose improved overall patient satisfaction, perceived effectiveness, convenience and may have potential cost advantages.

Further data on the development of anti-drug antibodies (ADAbs) to biologic therapies for psoriasis have also emerged since the 2011 publication. Biologics – even those that are fully humanized – have the ability to induce an immune response and produce ADAbs (21–24). Immunogenicity may be affected by a number of factors, including patient characteristics, route of administration and dosing interval, as well as the molecular structure of the drug itself (21). This issue has generated much debate, and while we do not yet have all the answers, the ability to maintain long-term treatment may be affected by the development of immunogenicity.

Opinion was divided across our group on the impact of immunogenicity on patient management; with some experts stating that it was the biggest barrier to long-term successful treatment although others who do not measure ADAbs in routine practice were less sure of the relevance. Several recent studies describe the potential impact of immunogenicity on patient outcomes. In Menting *et al*, the presence of ADAbs was strongly correlated with reduced serum concentrations of adalimumab, which in turn significantly reduced clinical response (25). None of the patients with high levels of ADAbs achieved a significant clinical response and, after 1 year, 46% of the 59 patients had developed antibodies. ADAbs also had an impact on clinical decision making as shortening dose intervals in an attempt to overcome a lack of efficacy was less useful in patients with ADAbs (25). In Takahashi *et al,* drug trough levels of adalimumab or infliximab were positively associated with PASI response and were significantly lower in patients with ADAbs.(26) In a recent systematic review, the incidence of of ADAbs reported in clinical trials against infliximab, etanercept, adalimumab and ustekinumab was 5.4–43.6%, 0–18.3%, 6–45% and 3.8–6% of patients, respectively. Anti-infliximab and anti-adalimumab antibodies were associated with lower serum drug concentrations, and decreased treatment response. The presence of anti-ustekinumab antibodies was also associated with lower PASI responses, and most of the anti-ustekinumab antibodies detected were neutralizing. ADAbs against etanercept were all non-neutralizing and were not associated with effects on clinical response (27). Patients who lose their response can be switched to another biologic in the same class, or to one with a different mechanism of action. Treatment algorithms based on drug-level testing and ADAb testing may be useful in clinical practice to help physicians decide the best course of action for these patients (23).

Considerations for biologic use in Africa and the Middle East

Tailored treatment

Patient needs vary according to individual patterns of disease and the impact of different environmental and social factors (28–31). Recent expert opinion suggests there is a need for more individualized treatment for psoriasis patients according to their specific needs (28,32,33), and that the ability to prescribe intermittent as well as continuous biologic treatment may be desirable for the patient, physician and healthcare system. As psoriasis is a life-long disease, the ability to adapt treatment to accommodate psoriasis patients' life events has been increasingly recognized, and physicians understand that there are many reasons why patients may need to stop and restart therapy (28).These can include planned events such as elective surgery, planned pregnancy or holidays, but also unplanned events such as severe infections. Those patients who achieve remission and remain stable may decide that they wish to have a break from treatment while their skin is clear and so a pattern of flexible treatment may also better suit the naturally fluctuating disease course of psoriasis. There are important differences in the biologic agents in this regard.

All of the experts had experience of needing to pause biologic therapy in some of their patients, as detailed in Table 1. Attitudes

Table 1. Overview of expert attitudes from three countries in Africa and the Middle East towards pausing biologic treatment.

How frequently do you have to pause biologic treatment in your patients?	In what circumstances do patients themselves request to pause treatment?	How confident are you and your colleagues with pausing and restarting biologic treatment?
Biologic treatment is paused as a result of infection, adverse allergic reactions, changes in lab results and pregnancy	If they reach skin clearance or pregnancy	We are reasonably confident
Infrequently	When the drug becomes ineffective	Confident enough
Often	In cases of complete remission, due to fear of adverse events, or travel	Confident with etanercept but otherwise it depends on the biologic
Typically, twice per year due to infection (mostly viral)	Most pauses are a result of financial constraints	I prefer not to unless there is a valid reason.
Quite infrequently	Pregnancy	Quite confident
I try not to but in cases of patient travel, surgery or pregnancy treatment will be paused	For those traveling, planning for pregnancy	Becoming more confident based on available data

towards therapy pause varied among both physicians and patients. There is evidence that patients themselves desire treatment breaks, either because they have achieved remission or because they have concerns about adverse events or the cost of continuous treatment. Others may wish to travel or plan a family. In countries where biologics are reimbursed for continuous use by the healthcare providers, there are generally fewer requests for treatment breaks than where patients pay for their own treatment.

While patients may ask for treatment breaks for a variety of reasons, dermatologists may not always be in favor of stopping treatment, largely due to concerns about possible relapse and subsequent difficulties in regaining response. Stopping and restarting therapy is not recommended for certain biologics such as infliximab, adalimumab or ustekinumab, although physicians may still adopt this approach in their clinical practice. However, there is strong evidence to support the strategy of stopping and restarting etanercept, with the ability to regain clinical response once treatment is restarted. This approach is included in the product label for etanercept (34). It was agreed that even the existing international guidelines do not offer clear strategies for intermittent treatment. The group's recommendation is that physicians should consider individual patient factors in every case. Disease severity is stable and the history of response to previous therapies are important factors when deciding to stop biologic treatment alongside how many treatments the patient has received and how many alternative therapies are available in case of loss of efficacy upon restarting. A patient's history of adherence and their treatment preference, as well as age, gender and quality of life should also be considered with any co-morbidities that could possibly be affected by treatment breaks. Efficacy and safety should always be taken into account ahead of cost. Additionally, it may be appropriate to refer patients to other specialties to manage their co-morbidities such as a rheumatologist for those with joint symptoms, a cardiologist for those with high cardiovascular risk factors, an endocrinologist for metabolic syndrome and a psychologist/psychiatrist for depression.

Long-term treatment

Long-term data are available for biologics showing efficacy up to 5 years in clinical trials (35,36). Data from real-world experience and biologic registries highlight that there are differences in drug survival between different biologic agents used for psoriasis (37–41). The OSCAR study found that etanercept has the longest drug survival rate among the TNF inhibitor biologic agents (1,565 days; $p < 0.001$) over adalimumab (1,056 days) and infliximab (1,120 days) (38). In a further sub-analysis, the group reported patients on an intermittent treatment regimen with etanercept maintained a longer overall treatment duration compared with those on a continuous regimen, indicating that flexibility is a desirable attribute for TNF inhibitor treatment (39). In the OBSERVE-5 registry, BSA, PGA and DLQI were all improved and sustained over 5 years of etanercept treatment (40). The DERMBIO registry also showed longer drug survival for ustekinumab compared with the TNF inhibitors (37).

Cost-effectiveness

One of the key challenges for several countries in the region was reimbursement of biologic treatment by insurance companies or third payers such as social security and Ministries of Health. As a result, differences were seen between dermatologists from countries such as Saudi Arabia and Lebanon regarding the significance given to biologic cost-effectiveness in the treatment decisions. Economic data are difficult to extrapolate between countries due to differences in pricing and healthcare systems; however, European studies have shown that the ability to use etanercept intermittently increases its cost-effectiveness (42,43).

Co-morbidities

Almost all patients with moderate-to-severe psoriasis will have at least one co-morbid condition. Apart from PsA, the most common co-morbidities seen in psoriasis patients in clinical practice are metabolic syndrome, obesity and depression. Diabetes – a major component of metabolic syndrome – is already common in many countries in the Middle East (44), and so may have a higher incidence among psoriasis patients than in other regions.

It is well documented that up to 42% of psoriasis patients will develop PsA (45–48) – a spondyloarthropathy associated with rapid, progressive and irreversible structural damage to joints (45,49,50). Up to 40% of these cases go undiagnosed (51), yet early diagnosis of PsA is critical for prevent permanent joint damage and disability and to achieve good clinical outcomes. A recent expert consensus recommended that all psoriasis patients should be examined at least annually for signs and symptoms of PsA (52). As in other areas, there is little Africa and the Middle East-specific guidance for the management of psoriasis patients with co-morbidities and few local registries collecting data on local patients (53). However, measures are in place to try and address this and a co-morbidity group has been established in the LEVANT area and is currently working on recommendations to screen for all psoriasis co-morbidities including PsA.

There are currently several biologic therapies approved for use in both moderate-to-severe psoriasis and PsA in Africa and the Middle East. The main efficacy data from the key Phase 3 trials in PsA are summarized in Table 2.

Safety considerations in Africa and the Middle East

Biologic agents have immunomodulatory effects, and this can mean that patients are potentially more susceptible to infections

Table 2. Biologic efficacy data in PsA.

	Patients (N)	Dose/design	Patients achieving outcomes (%) ACR 20	ACR 50	ACR 70
Etanercept					
Sterry 2010 (74) (PRESTA)	379	50 mg BIW/QW for 24 weeks	69.0%	51.8%	34.6%
	373	50 mg QW/QW for 24 weeks	71.7%	53.6%	36.7%
Adalimumab					
Mease 2009 (75) (ADEPT)	289	40 mg EOW for 48 weeks	58.7%	42.7%	27.8%
Infliximab					
Kavanaugh 2007 (76) (IMPACT 2)	100	5 mg/kg at weeks 0, 2, 6, and q8w for 24 weeks	54.0%	41.0%	27.0%
Ustekinumab					
Gottlieb 2009(77)	59	45 mg or 90 mg for 12 weeks	42.0%	25.0%	11.0%
Ritchlin 2014 (78) (PSUMMIT2)	103	45 mg at week 0, week 4, q12 weeks for 24 weeks	43.7%	17.5%	6.8%
	105	90 mg at week 0, week 4, q12 weeks for 24 weeks	43.8%	22.9%	8.6%
McInnes 2013 (79) (PSUMMIT1)	205	45 mg at week 0, week 4, q12 weeks for 52 weeks	42.4%	24.9%	12.2%
	204	90 mg at week 0, week 4, q12 weeks for 52 weeks	49.9%	27.9%	14.2%

ACR: American College of Rheumatology; PASI: psoriasis area severity index; BIW: twice weekly; QW: once weekly; EOW: every other week.

or the reactivation of latent infections. In the Spanish registry BIOBADADERM, psoriasis patients treated with a biologic therapy had an increased risk of TB infection (54). While TB has been eradicated in many Western populations, TB infection remains prevalent in the Africa and the Middle East region and is an important factor when considering initiation of a biologic agent. The expert group recommendation is to always carry out TB testing in new patients being considered for a biologic, with yearly testing thereafter. For patients with a positive TB test result, anti-TB treatment should be initiated according to local policy. In some areas, isoniazid treatment would be given for 9 months, with biologic therapy initiated after 1-month of anti-TB therapy (55). Data are only beginning to emerge on the drug-specific risk of TB infection in psoriasis (56) but results support previously published rheumatoid arthritis registry data that etanercept confers a lower risk for TB infection than infliximab or adalimumab (57). Diabetes – a common co-morbidity in psoriasis patients – can also be a risk factor for TB infection (58). This makes screening even more important in such patients.

With ~2–5% of patients in the Middle East chronically infected with hepatitis B (59), hepatitis screening should also be performed before TNF inhibitor treatment is initiated.

All of the biologics available for psoriasis should be discontinued immediately if a patient develops a serious infection. Etanercept has the shortest half-life of available biologics (~70 h), which means patients can stop treatment quickly if an infection does develop.

Educational needs and referral strategies for psoriasis patients

The World Health Organization recently acknowledged psoriasis as a "chronic, non-communicable, painful, disfiguring and disabling disease for which there is no cure" (60). Despite this there is a generally low level of awareness among physicians in Africa and the Middle East about psoriasis and its associated co-morbidities. Psoriasis patients have increased mortality compared with age-matched controls, and are at increased risk for serious cardiovascular complications (61,62). There is therefore a need to improve disease awareness and educate dermatologists about appropriate psoriasis treatment strategies and screening for co-morbidities. Likewise, local clinical trials and registries could be established in order to collect information about the specific patient profiles in Africa and the Middle East. At present, referral strategies are determined by individual clinics and hospitals, and there are no national systems in place to ensure that patients receive specialist care. Patient associations and support groups may be helpful in raising awareness of the disease, and there are moves in Lebanon to establish a Psoriasis Patient Association. Although psoriasis is a common disease patients can feel isolated; support groups can be very significant in reassuring patients and educating them about their condition and the availability of effective treatments.

Discussion

Psoriasis is a life-long inflammatory systemic disease associated with considerable and serious co-morbidities that may affect each individual patient differently (63,64). Severe psoriasis can be very disabling, with an impact on quality of life comparable to that of heart disease or cancer (65,66). Significantly, decreased productivity and increased health-resource use lead to a real economic impact both for patients and the wider society (67,68).

It is now well accepted that psoriasis is linked to co-morbidities such as obesity, cardiovascular disease and PsA (19,61,69,70). Psoriasis represents a significant problem for dermatologists and healthcare professionals as well as patients and their families.

Biologic drugs have significantly improved patient outcomes and raised expectations of psoriasis treatment (71–73), and these biologic drugs have opened up new treatment options for patients and physicians in the Africa and the Middle East region. Yet this literature review and physician survey has highlighted that significant challenges remain in the treatment and management of psoriasis patients in Africa and the Middle East. Even experienced dermatologists do not always prescribe biologic therapies in eligible patients, and local barriers may limit awareness of and access to modern treatments. Real-life management decisions are often not straightforward (33). Psoriasis imposes a significant burden on patients and physicians; however, the large choice in biologic agents can alleviate this burden and offer patients an improved quality of life and work productivity. Each patient is an individual and patient characteristics should be considered when deciding which therapies to use, with the need for flexible treatment and common co-morbidities such as PsA playing a key role when it is present. It is possible to achieve sustained clinical efficacy over the long-term with both continuous and intermittent treatment regimens for etanercept, and its safety profile is now well established. Immunogenicity could play an important role in the long-term control of psoriasis; however, standardized methods that allow the measurement of ADAs and to differentiate between primary non-responders secondary to these antibodies or as a result of the biologic itself (in the case of a non-response with negative ADAs) are required for the future. This strategy will allow dermatologists to make an accurate decision regarding how to switch between TNF inhibitors and between a TNF inhibitor and a different mechanism of action. In the case of secondary non-responders, measurement

of ADAs will allow dermatologists to switch early to another treatment.

The varying safety profile of the different biologic agents is also relevant for a region where TB, hepatitis and other infections are more prevalent than in other regions, although it should be noted that the overall safety profile for all biologics is good. Long-term drug survival is also important given that psoriasis is a chronic condition likely to require many years of treatment.

The development of specific local guidelines for the treatment of psoriasis and PsA could be a step towards understanding the distinct patient profiles in the region. New screening tools for co-morbidities are also needed to optimize the management of psoriasis. Physicians should be aware of the problem of non-adherence to systemic treatments in chronic diseases; drivers for non-adherence should be identified and tailored solutions should be adopted to improve the level of adherence. Likewise a patient-centered approach to psoriasis care may help optimize outcomes and reduce the physical, social and economic burden of psoriasis and psoriatic arthritis in Africa and the Middle East.

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