REVIEW ARTICLE

Psoriasis and Treatment: Past, Present and Future Aspects

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The management of psoriasis has evolved considerably over the past 100 years. This has occurred in parallel with our understanding of the pathogenesis of this common, complex and enigmatic disease. It should be celebrated as an outstanding example of successful translational research. With precise targeting of immune pathways for the treatment of psoriasis with new biologics and small molecules has come the realisation that the most effective approach to patient management is a holistic one which encompasses the biopsychosocial nature of the disease. This involves a stratified medicine approach to identifying the best drug for an individual allied to patient education, screening for comorbidity, and regular review as both the clinical presentation and the patient's needs will change over time. Although there is not yet a cure for psoriasis – the whole person, systems approach to patient management, that is in part dependent on early intervention, should help to ensure an optimal outcome.

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SIGNIFICANCE

Psoriasis is a common and disfiguring chronic skin condition. Over the past 100 years, our understanding of the disease has improved and as a direct result, more effective therapies have been developed. In addition to the cutaneous manifestations, it is associated with an increased risk of psoriatic arthritis, depression and cardiovascular disease. The best approach to care is an individualised one which focuses on improving the physical symptoms of the rash while proactively screening for and treating any associated comorbidities to minimise the impact of the disease and empower patients to live well.

This psoriasis-themed edition of *Acta Dermato-Venereologica* provides an opportunity to reflect on the progress which has been made in the treatment of psoriasis over the intervening 100 years since the journal was established in 1920.

The first volume of the journal featured a patient with 'psoriasis universalis' (1); a case which would fit with our current definition of erythrodermic psoriasis. The patient was treated with, a to us unusual, combination of bran baths, borvaseline emollient and injections of sterilised milk. An improvement was noted after the third cycle of injections, at which point cignolin (dithranol) was introduced to treat the remaining plaques. Fortunately, therapies for patients have evolved greatly in terms of efficacy, safety and tolerability. Over the past century therapies for psoriasis were more commonly discovered by chance and recommendations were largely based on anecdote. Today, serendipity still plays a role in the advancement and discovery of therapies but the reductionist approach to targeted therapies and evidence-based guidelines hold sway (2).

One hundred years ago, psoriasis was recognised as a relapsing and remitting skin condition for which temporary remission, but not cure, was possible with treatment (3). Although a cure remains elusive, treating psoriasis as an isolated skin disease is widely viewed as an outdated approach. The condition is now accepted as a systemic immune-mediated inflammatory disease associated with several comorbidities including psoriatic arthritis, mood disorders and cardiovascular disease. When selecting therapy, several factors should be considered in addition to the extent and clinical severity of the cutaneous involvement. These include psoriasis phenotype and previous treatment history, clinical severity and psychosocial impact, presence of psoriatic arthritis and other comorbidities, concomitant medications, conception plans and of course individual preferences and treatment goals. An effective approach to treatment is holistic, recognising the multi-faceted nature of the disease, and should be flexible as this chronic disease evolves and patient needs change over time.

The evolution of psoriasis treatment over the past century is an excellent example of successful translational research whereby an enhanced understanding of the pathogenesis of the disease has facilitated the development of increasingly precise targeting of therapies. Biologics are the proof of concept in this modern approach to drug design and development and the management of patients with moderate-severe disease has been transformed by these therapies. Complete skin clearance or psoriasis area and severity index (PASI) 100 has become a realistic treatment goal with use of the recently available anti-interleukin (IL) 23p19 therapies. Despite this progress, patients face many challenges including timely access

to appropriate care; the cost of under-treatment to the individual and to society remains and is considerable (4).

This review outlines the major treatments used for psoriasis over the past 100 years, focusing on important milestones through the decades. It illustrates a shift in approach from serendipity to science, as modern-day drug development is based on targeting key effector molecules in psoriasis, and a shift to a whole patient approach to care.

1920's

Even a hundred years ago, a variety of treatments, both systemic and topical, were available for psoriasis and salicylic acid, coal tar and dithranol preparations were all in use. **Fig. 1** illustrates those therapies which were available 100 years ago and tracks major therapeutic developments to the present day.

In the 19th century, arsenic became established as a popular treatment for psoriasis. It was trialled for a variety of dermatological conditions but appeared to be most effective for psoriasis. It was taken orally or applied topically – and even added to spa water. A narrow therapeutic range meant it was usually ineffective at low doses, and high doses were associated with clinically significant ocular and gastrointestinal tract disturbances (5). With more widespread prescription, the adverse effects associated with chronic use became more apparent. Cutaneous adverse effects including hyperpigmentation, keratotic and cancerous growths were noted towards the end of the 19th century but it continued to be used to treat psoriasis during the first half of the 20th century. Today, arsenic toxicity is well recognised (6).

Balmanno Squire first described the use of Goa powder (chrysarobin), a forerunner of dithranol (anthralin), for the treatment of psoriasis and published this in the British Medical Journal in 1876 (7). Produced from the araroba tree in Brazil, Goa powder had been used for centuries to treat fungal infections. Squire used Goa powder for a patient with psoriasis who he thought had tinea corporis; the psoriasis cleared prompting his accidental discovery of it as an effective treatment for the condition. Importing this product from Brazil to Europe became difficult during World War 1; in 1916, a synthetic version known as cignolin or dithranol was synthesized which seemed more efficacious than the natural variant. There is a correlation between efficacy and side-effects of irritancy and discoloration of skin, nails, clothes. In 1953, Ingram suggested using dithranol as a photosensitiser with ultraviolet-B radiation (UV-B) (8). The use of short contact dithranol became popular in the early 1980's. This involves applying a concentrated version of dithranol which is washed off after a few minutes and so is more practical and acceptable for patients. Nowadays dithranol is used only rarely by outpatients with most cases being treated in day treatment centers or as inpatients.

X-rays were first used to treat psoriasis at the beginning of the 20th century. Carcinogenic and other side effects became apparant over time, and so this method was phased out by the 1950's (3, 9). The beneficial effects of heliotherapy in treating psoriasis were first reported in 1923 (10), although patients had been aware, for centuries, that sunlight improves their psoriasis. In 1925, Goeckerman used a high-pressure mercury lamp to produce artificial broadband UV-B and demonstrated that the effect of UV-B was enhanced with prior application of crude coaltar as a photosensitiser (11).

1950's

Corticosteroids were discovered in 1950 and two years later, the first report of a topical steroid (17 hydroxycorticosterone-21-acetate) used to treat two patients with psoriasis was published; it did not have any noticeable

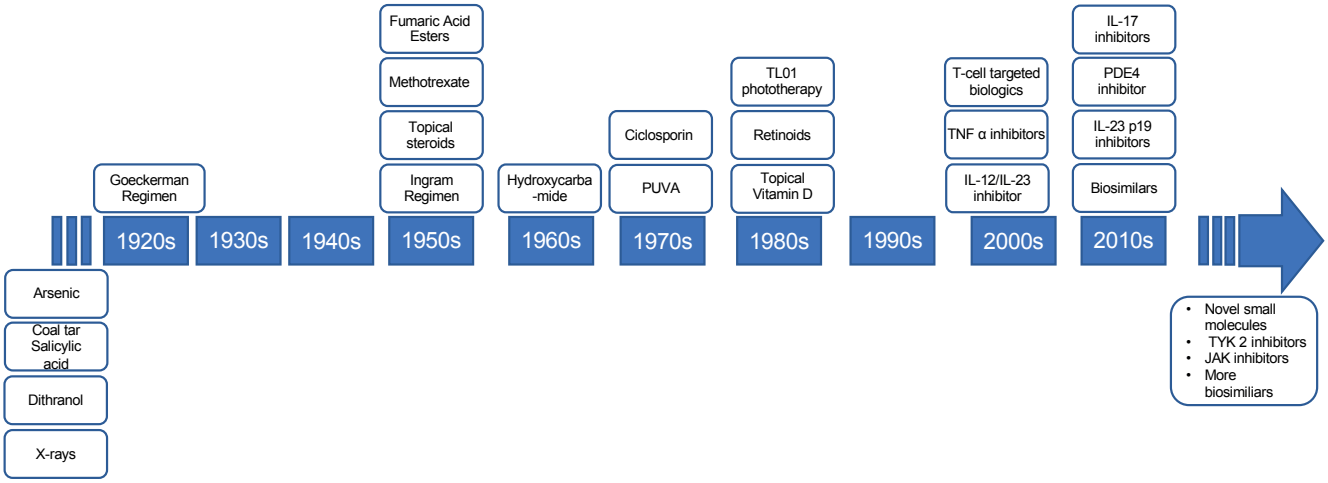

Fig. 1. Advances in the treatment of psoriasis over the past century. This timeline illustrates the major pharmacological advances which have occurred in the management of psoriasis over the past 100 years. It also speculates as to what may be the important therapies in the near future. IL: interleukin; PDE: phosphodiesterase; PUVA: psoralen plus ultraviolet (UV)-A; TNFα: tumour necrosis factor alpha; TYK: tyrosine kinase; JAK: janus kinase.

effect which may have been due to its low potency (12). Following this report, the structure of the compound was modified and by the end of the 1950's, a variety of local and systemic corticosteroid drugs had been developed. Prednisolone and triamcinolone were both shown to be moderately effective when taken orally (3). In the early 1960's, potent topical steroid preparations were developed including betamethasone 17-valerate (Betnovate®) and fluocinolone acetonide (Synalar®) marking a significant breakthrough in the treatment of dermatoses in general. We now know that potent steroids only suppress psoriasis temporarily. Today, topical corticosteroids are the acknowledged first line recommended topical therapy either alone or in combination with vitamin D analogues (2). They are known to have an anti-inflammatory, immunosuppressive, and anti-proliferative mechanism of action in psoriasis. Steroid-related side effects are well recognised however, and include skin atrophy with increasing potency, tachyphylaxis, suppression of the pituitary-adrenal axis, and a rebound phenomenon which may lead to psoriasis becoming unstable or pustular.

Methotrexate was first used to treat psoriasis in the early 1950's. Aminopterine, a folic acid inhibitor which had been used to treat leukaemia, was shown to suppress arthritis experimentally. Thus, it was trialled in a group of patients with rheumatoid arthritis. One of these patients had psoriasis which improved markedly. The authors of this original report proposed that aminopterine probably worked via direct effect on epithelial cells; at the time, psoriasis was thought to be a disorder of keratinocytes (13). Ametopterine (methotrexate) a next generation folic acid antagonist was subsequently developed; it was shown to be as effective as aminopterine but less toxic (14). Methotrexate is currently recommended as first line therapy for most people with psoriasis who are eligible for systemics. It is also effective for psoriatic arthritis (15). It is typically given as a once weekly oral dose. Folic acid supplementation is recommended when prescribing methotrexate. Folic acid use may also decrease the gastrointestinal and mucosal side-effects of methotrexate (16) whilst having a protective effect against hepatotoxicity (17). Its specific mechanism of action remains uncertain. It is thought to exert an anti-inflammatory effect via adenosine pathways. Some of the immunomodulatory effects are mediated through the inhibition of nucleic acid synthesis in keratinocytes and activated T cells (18). A recent meta-analysis showed that 45% of patients achieve PASI75 at primary endpoint (12 or 16 weeks, respectively) (19). The side effect profile of methotrexate is well characterised, in particular the hepatotoxicity risk. Appropriate patient selection to minimise this risk is important (2) and subcutaneous administration may reduce gastrointestinal side-effects and enhance efficacy (20).

The German chemist Schweckendiek was the first to use fumaric acid esters FAE to treat psoriasis in the late 1950's. He postulated that psoriasis occurred due to a deficiency in fumaric acid levels leading to defects in the Krebs citric acid cycle, and that oral supplementation of fumaric acid might neutralize these defects. He suffered from psoriasis, and used esters of fumaric acid in self-experimentation (21). The drug was subsequently modified to produce Fumaderm®, which comprises dimethyl fumarate (DMF), and calcium, magnesium, and zinc salts of monoethyl hydrogen fumarate; licensed for oral use in Germany since 1994. A second oral product, Skilarence® (dimethyl fumarate as a single acid ester), was introduced to the European market for the treatment of psoriasis in 2017. The mechanism of action of (FAE) remains unclear, but evidence suggests that it has nothing to do with the Krebs cycle. Recent systematic reviews have investigated the efficacy and safety of FAE using data from randomised controlled trials (22, 23). Meta-analysis showed that a PASI50 response rate at 12–16 weeks was achieved by 64% receiving FAE compared to 14% in the control group – it was not possible to calculate PASI75. It is ineffective for treating psoriatic arthritis. Of note, 8–39% of patients discontinue FAE treatment owing to adverse events, mostly relating to intolerable gastrointestinal or flushing complaints (23).

1970's

Psoralens, photosensitisers extracted from plants, have been used for centuries to manage skin conditions such as vitiligo. The beneficial effect of topical and the subsequent use of oral psoralens combined with UVA (PUVA) in treating psoriasis was first reported in 1973 (24) and subsequently became widespread (25). It was the most effective systemic therapy in use for psoriasis in the 1980s. PUVA can increase the lifetime risk of cutaneous squamous cell carcinoma, and this limits its use (26); indeed the use of PUVA has diminished markedly in recent years as it has been usurped by narrow band UVB, which was introduced in the 1980s after it was found to be more effective than broadband UVB in the treatment of psoriasis (27, 28).

In 1979 it was reported, serendipitously, that ciclosporin improved psoriasis in patients with psoriatic arthritis (29). By this time, it was already known to be an immunosuppressant drug which exerted its effect through inhibition of T-cell proliferation and had transformed outcomes in solid organ transplant recipients (30), but the mechanism of action in treating psoriasis remained unclear. A few years later, the active selective recruitment of T-helper cells into psoriasis plaques was demonstrated (31, 32). The authors proposed that psoriasis should be considered a T-cell-mediated disease and this hypothesis was subsequently proven by the remarkable efficacy of ciclosporin in its treatment (33). Today, there is substantial evidence for efficacy of ciclosporin in psoriasis vulgaris (34) but its use is limited by a relatively narrow therapeutic index. Nephrotoxicity and hypertension

are the most significant common risks of ciclosporin. Nephrooxicity risk is directly related to the dose and duration of ciclosporin (35). Thus, single or intermittent short courses of up to 16 weeks are recommended to limit nephrotoxicity (34, 35). Ciclosporin is particularly effective for patients who need rapid or short-term disease control (for example a psoriasis flare), have palmoplantar pustulosis or are considering conception and systemic therapy cannot be avoided (2).

The discovery of ciclosporin marked a turning point in the history of psoriasis treatment and the direction of future translational research as it became clear that a deeper understanding and subsequent modulation of the immune system would lead to more effective disease control.

1980's

Vitamin D analogues were investigated in the 1980s for a range of dermatoses. Calcipotriol, a vitamin D3 analogue, was shown to be effective in reducing proliferation and inducing differentiation of epidermal keratinocytes, indicating potential efficacy when used topically for psoriasis (36, 37). This therapy was subsequently shown to be significantly more effective than either dithranol (38) or tar (39). Although not as effective as potent topical steroids, calcipotriol has the advantage of not being subject to the same side-effects. Calcipotriol may protect against corticosteroid-induced dermal atrophy (40). Local irritation at the site of application affects up to 20% of patients (41) and this may lead to discontinuation. The vitamin D analogue calcitriol tends to be less irritating than calcipotriol and so may be better tolerated on face and flexural sites (42). Combination of calciptriol and betamethasone valerate as either ointment, cream, gel, or, more recently, a foam spray preparation, has proven to be a highly effective topical preparation for psoriasis (43).

The importance of vitamin A in maintaining healthy skin was recognised over 100 years ago. Synthetic vitamin A drugs, retinoids, were subsequently developed and trialled for a variety of skin diseases. Etretinate was found to improve psoriasis but this was replaced by acitretin, its pharmacologically active metabolite, in the late 1980s, because of a more favourable and less lipophilic pharmacokinetic profile. The precise mechanism of action is not understood. It is believed to interfere with epidermal growth factor receptor gene expression which reduces epidermal cell proliferation and differentiation to a normal rate (44). Additional anti-inflammatory effects may be mediated through nitric oxide (45).There is considerable variability in reported effectiveness of acitretin and anecdotally, it tends to work best for the less common pustular and erythrodermic variants of psoriasis (46). Acitretin may be combined with PUVA which is more effective than PUVA alone, reducing the number of PUVA treatments needed and hence UVA exposure (47). The use of acitretin is limited by its safety profile. It is highly teratogenic and pregnancy should be avoided for at least 2 years after the last dose. These days, acitretin is recommended for adults and in exceptional cases for children and young people if other conventional systemics (ciclosporin and methotrexate) are not appropriate or have failed, and for cases of pustular psoriasis (2).

With the development of an increasing number of systemic therapies, it became apparent that a valid and objective approach to the assessment of cutaneous disease severity and response to treatment was needed for psoriasis. Fredriksson & Pettersson created the PASI in 1978 as an objective means to evaluate the clinical efficacy of retinoids for psoriasis (48). Today, it is the most widely recognised outcome measure in psoriasis management. The Dermatology Life Quality Index (DLQI), the first dermatology-specific health-related quality of life questionnaire, was published several years later in 1994 (49). Although not specific for psoriasis, it is widely used to assess the subjective effectiveness of psoriasis treatments and their effect on quality of life.

BIOLOGICS ERA

Biologics are a subgroup of drugs comprised of large complex protein molecules including monoclonal antibodies and receptor fusion proteins. Unlike the traditional systemics which are taken orally, these are administered parenterally – as they would otherwise be degraded by the gastrointestinal tract. These target specific components of the immune system that are involved in psoriasis pathogenesis.

Biologics are indicated for moderate-severe psoriasis which has not responded to conventional systemic therapies. This licensing reinforces the current stepwise approach to psoriasis treatment. Patients with mild or limited extent disease are typically prescribed topical therapy in the first instance. If this is not sufficient, they are deemed to have moderate-severe disease and phototherapy or conventional systemic therapies (methorexate, ciclosporin, acitretin) are used next. If these fail, small molecule therapies (FAEs, apremilast) or biologics are indicated. Unfortunately, we do not yet have the tools in clinical practice to predict which patient will respond favourably to a given drug. As a result, between 11 and 35% of patients do not respond sufficiently to their first biologic drug during the first year of treatment, either because the drug is not effective or adverse effects develop (50).

2000's

T-cell targeted biologics

Research on the mechanism of action of ciclosporin in treating psoriasis (29) affirmed it being a T-cell-mediated

disease, and subsequent mouse models added further evidence to the theory that immune cells are the primary effector cells in driving the disease (51). Ensuing from this, the first biologics to be developed for the treatment of psoriasis targeted T cells.

The first was alafacept, which was approved for psoriasis use in 2003. This is a human lymphocyte function-associated antigen (LFA)-3/immunoglobulin (Ig) 1 fusion protein. It binds to CD2 molecules on the surface of activated T cells, blocking their co-stimulation by antigen presenting cells. It selectively targets memory-effector T cells, blocking their activation and migration (52, 53). Despite high hopes resulting from the known mechanism of action of this drug and what was known about the pathogenesis of psoriasis at that time, the results of phase III studies indicated a modest overall efficacy (54, 55). The overall PASI75 response rate was 33%. Median duration of remission (time to retreatment or maintenance of PASI50) was 7 to 10 months in phase II and III studies (56). In 2011, alefacept was withdrawn from the market as it had become clear that more efficacious and cost-effective options had become available.

Efalizumab was the first biologic to be approved in the UK for the management of psoriasis in 2003. This drug is a humanized monoclonal IgG1 antibody, directed against CD11a, the α-subunit of LFA-1. This inhibits T-cell trafficking into the skin. In phase III studies, the PASI75 response rate was approximately 30% when compared to placebo (57, 58). Increasing the duration of treatment from 12 to 24 weeks resulted in a PASI75 of 44% (58). Post-marketing drug surveillance revealed an association between long-term treatment with efalizumab and progressive multifocal leukoencephalopathy (PML) which is a rare but life-threatening infection of the central nervous system (59). As a result, efalizumab was withdrawn from the market in 2009. This reminds us of the importance of monitoring drug safety in the post-marketing phase.

Tumour necrosis factor-α inhibitors

Tumour necrosis factor (TNF)-α is recognised as a key effector cytokine in chronic immune-mediated inflammatory diseases, including psoriasis.

Etanercept was the first TNF-α inhibitor approved for treatment of psoriasis in 2004. It is a recombinant human TNF-receptor fusion protein. Each molecule can bind two TNF-α molecules. Phase III studies show that 100 mg weekly results in PASI75 at week 12 in 47–49% compared with placebo (60–62). Infliximab, a chimeric IgG1 monoclonal antibody which can bind to and neutralise soluble and membrane-bound TNF-α was approved for the treatment of severe psoriasis in 2006. This derived from the observation that it cleared the concomitant psoriasis of a patient in whom it had been administered for the management of Crohn's disease. Two phase III studies reported that intravenous infliximab 5 mg/kg at week 0, 2, and 6 resulted in PASI75 responses at week 10 of 75.5% and 80% compared with placebo (63, 64). This level of efficacy had not previously been recorded with any treatment for psoriasis. Adalimumab was approved for the treatment of psoriasis in 2005. Similar to infliximab, adalimumab is a fully human monoclonal antibody of the IgG1 isotype. PASI75 response rates of around 70% have been reported in clinical trials (65).

A meta-analysis has confirmed that infliximab is the most efficacious drug in this class in terms of PASI, followed by adalimumab (66). However, infliximab is associated with an increased risk of serious infection (67) and infusion reactions can occur.

Targeting TNF-α is particularly effective for treating psoriatic arthritis. Therefore, adalimumab is currently the recommended first line biologic for psoriasis with psoriatic arthritis (68). There are rare but potentially severe adverse events associated with this drug class including multiple sclerosis, congestive heart failure, opportunistic infection such as tuberculosis, and lupus. The risk of developing neutralizing anti-drug antibodies is well described for this class which in turn is associated with reduced clinical response to infliximab and adalimumab treatment (69).

Anti-TNFα therapies continue to develop and evolve. Certolizumab pegol (CZP) was licensed for psoriasis in 2018, and psoriatic arthritis in 2013. It is the only biologic agent with clinical trial data in its label supporting potential use in both pregnancy and breastfeeding. Prospective studies showed a lack of placental transfer of CZP from mothers to infants (70), and no to minimal transfer from plasma to breastmilk (71). The adalimumab and etanercept labels have recently been updated to allow potential use during pregnancy while acknowledging that they may cross the placenta (72). These recent developments have brought the issue of managing psoriasis in women of childbearing age into sharper focus, highlighting the specific challenges faced by this large group.

Ustekinumab anti-IL12/IL-23

Psoriasis was the first inflammatory disease for which ustekinumab was licensed by the US Food and Drug Administration (FDA) in 2009. It is a human IgG1 monoclonal antibody that targets the shared protein subunit p40 of IL-12 and IL-23. PASI75 response at week 12 in phase III studies was 66% (73) and 76% (74) and this was maintained at week 28. For patients with a bodyweight ≤100 kg the dose of ustekinumab is 45 mg and with a body weight of >100 kg the dose is 90 mg.

Registry data show that ustekinumab has a longer drug survival compared to the anti-TNF-α therapies (50, 75). Due to its effectiveness, weight-based dosing and safety record – it is recommended as first line biologic

for patients with psoriasis without psoriatic arthritis in the UK (68).

2010's

The current consensus is that psoriasis is a disease driven by the IL-23/TH17 cell pathway. For this reason, current therapeutic strategies are now focused on the development of novel agents that disrupt IL-23 or IL-17 cytokine signalling.

Three IL-17 pathway antagonists have been approved for the treatment of psoriasis: secukinumab was the first approved in 2015, and since then ixekizumab and brodalumab have come to market. Ixekizumab and secukinumab target IL-17A, while brodalumab targets the receptor subunit IL-17RA. Both secukinumab and ixekizumab have been approved for psoriatic arthritis. Phase III studies have demonstrated favourable efficacy and safety profiles. For the first time, significant numbers of patients are achieving PASI90 or PASI100 with treatment. In the CLEAR trial nearly 80% of patients treated with secukinumab achieved a PASI90 response at week 16 compared with only 58% in a comparison cohort treated with ustekinumab (76). The available safety information is overall reassuring, but there are specific adverse events associated with IL-17 inhibition, including increased risk of mucocutaneous candida and a slightly increased risk of developing inflammatory bowel disease (77). Four suicides were reported in clinical trials for brodalumab which raised some concern, but no causal relationship was demonstrated when these cases were reviewed (78). Bimekizumab is a novel drug in this class as it inhibits both IL-17A and IL-17F. The result of phase 3 comparative studies in patients with psoriasis and psoriatic arthritis are pending.

The latest biologic group to be licensed for the management of psoriasis are those which specifically target the p19 subunit of IL23. Three drugs have been licensed: guselkumab, rizankizumab and tildrakizumab. Guselkumab, the first of the 3 to be approved by the FDA in 2017, was compared to adalimumab in the VOYAGE 1 and 2 clinical trials. The PASI90 response at week 16 was 73% versus 50% (VOYAGE 1) and 70% versus 47% (VOYAGE 2), confirming the superior efficacy of guselkumab (79, 80). Guselkumab also showed superior long-term efficacy based on PASI90 at week 48 when compared with secukinumab (81).

In phase 3 studies comparing rizankizumab to ustekinumab at week 16, PASI90 was achieved by approximately 75% of patients receiving risankizumab versus 45% receiving ustekinumab and 4% receiving placebo (82). Pivotal trials for tildrakizumab selected PASI 75 at week 12 as the co-primary outcome measure. In one study, 64% of those who received the study drug achieved PASI75 compared to 9% of those who received placebo. In a subsequent clinical trial, 61% who received tildrakizumab and 48% who received etanercept achieved PASI75 (83).

The selective IL-23 p19 inhibitors have proved to be highly efficacious in clinical trials and no specific safety concerns have been raised to date (84). Although the depletion of IL17 by the anti-IL 17 biologics class has been associated with an elevated risk of opportunistic infections, mucocutaneous candida infections, and triggering or worsening of inflammatory bowel disease; the IL-23 p19 inhibitors have not been associated with these side effects (84). This is thought to be because residual IL17 is produced by non TH17 cells such as innate lymphoid cells and mast cells, so function is not clinically impaired. In addition, no increase in rates of malignancy, major adverse cardiovascular events, demyelinating disorders, active tuberculosis or reactivation of latent tuberculosis infection have been reported, although these have been associated with other biologic drug classes (84).

The real test will be how IL23p19 inhibitors perform in the real-world clinical setting. In addition to PASI90 and PASI100, other novel outcomes have been assessed for these drugs. For example, the efficacy of withdrawal and retreatment with guselkumab was assessed in VOYAGE 2 and it was shown that few patients required retreatment by week 48 (80). Amongst patients treated with guselkumab, efficacy was maintained at 2 years with continuous therapy while efficacy improved amongst those who switched from adalimumab to guselkumab at week 52. Reassuringly, there was no significant increase in adverse event rate compared with rates through week 48 (85).

The recent increase in published head to head comparator studies amongst biologic therapies is a welcome addition to the literature as this provides more meaningful results than placebo comparator alone.

Apremilast is a small molecule therapy which was licensed in 2014 to treat moderate–severe psoriasis and active psoriatic arthritis. It inhibits phosphodiesterase (PDE) 4 and thus reduces expression of proinflammatory mediators such as TNF-α and IL-23 (86). The PASI75 response to apremilast 30 mg twice/day ranges from 29–41% at week 16 in clinical trials (87). It is moderately effective for both psoriasis and psoriatic arthritis, with an efficacy level comparable to methotrexate. Advantages include its oral administration and it is anti-inflammatory rather than immunosuppressant. It also has a favourable safety profile, laboratory monitoring is not required and a potentially advantageous weight loss effect (88). Gastrointestinal intolerance is the most common adverse effect reported in clinical trials – diarrhoea (18%) and nausea (17%) (89) and rates appear higher in real world clinical practice (90). Apremilast has potentially been associated with an increased risk of depression, although the incidence is low – caution and close monitoring is advised in patients with a history of depression.

RECENT THERAPEUTIC DEVELOPMENTS

A variety of small molecule oral and topical drugs are in development for psoriasis. Indeed, the majority of drugs in the clinical trial pipeline for psoriasis are small molecules. The drugs listed below interfere with the IL-23/TH17 cell pathway that is key in driving the disease.

Tofacitinib is an oral Janus kinase (JAK) inhibitor targeting JAK1 and JAK3, thus regulating immune response via interruption of intracellular signalling pathways involved in the pathogenesis of psoriasis. A recent meta-analysis showed that approximately one third of those receiving tofacitinib 5 mg twice/day and half of those receiving tofacitinib 10 mg twice/day achieve PASI75 at week 12–16. Results to date indicate that it is generally well tolerated in treating psoriasis (91, 92). Although of modest efficacy, the favourable safety profile is appealing. JAK show efficacy in the topical treatment of psoriasis as well as atopic dermatitis and may have utility in facial and flexural disease as they are without corticosteroid side-effects (91). Research into this new topical therapy is welcomed as there has not been very much development in this area in recent decades.

Tyrosine Kinase 2 (TYK 2) signalling pathways are implicated in psoriasis pathogenesis and recent Genome Wide Association Studies have identified TYK 2 as a "druggable target". This molecule is an intracellular signalling enzyme which can activate functional responses of interleukin-12, interleukin-23, and interferon receptors – key cytokine pathways in psoriasis pathogenesis. A recent phase 2 study of TYK 2 inhibitor therapy for moderate to severe psoriasis has shown promising results (93). Several different doses were trialled and the primary outcome measure was PASI75 at week 12. This was achieved by 75% of patients on the maximal dose of 12 mg daily. Trials of longer duration and with a larger population are required to determine the longer-term safety and effectiveness of this agent.

MANAGEMENT OF PSORIASIS AS A COMPLEX CHRONIC DISEASE

The management of a patient with psoriasis involves much more than selecting and prescribing the recommended drug. Effective chronic disease management demands a holistic and proactive approach. Management incorporates patient education, screening for comorbidity and adjusting therapy depending on changes in clinical presentation.

Patient education improves patients' understanding of psoriasis and imbues a sense of control (94) in addition to improving adherence and coping. Screening for comorbidity is included in some national guidelines for managing psoriasis (2). This is particularly important for psoriatic arthritis because early diagnosis and commencement of appropriate treatment goes some way to prevent irreversible joint damage (95). It is also important for the detection of risk factors for cardiovascular disease and mood disorders, both of which are highly prevalent amongst this group and contribute to the multi-morbidity complexity of psoriasis (96, 97).

Alcohol excess, smoking and obesity are more prevalent amongst patients with psoriasis and are predictors of poor outcome to systemic therapies. Pharmacovigilance registry data demonstrate that being either a current or ex-smoker, and high body mass index are associated with a reduced odds of achieving PASI90 at 6 months when treated with biologic therapy. This underscores the need for lifestyle management as such factors are modifiable (98). A recent systematic review indicated that weight loss can improve pre-existing psoriasis and psoriatic arthritis, and prevent the onset of psoriasis in obese individuals, highlighting the importance of this intervention as an adjunct in psoriasis management (99). Further investigation into the role of lifestyle management has been identified as a key research priority by the Psoriasis Association in their recently published priority setting exercise (100). Management of these lifestyle factors using motivational interviewing techniques as espoused by the Psoriasis Wellbeing (PsoWell™) (94, 101) programme is likely to play an increasingly prominent role as part of a more integrated approach to psoriasis management going forward.

Never before have there been so many treatment options for psoriasis. However, clinicians are often faced with a challenge when selecting which systemic or biologic drug to commence for their patient as it is not possible to predict which patient will respond to a given therapy. The resultant primary and secondary treatment failures are costly from a patient and socio-economic point of view. With this in mind, the PSORT (Psoriasis Stratification to Optimise Relevant Therapy) (102) consortium was established to develop predictors of clinical response to biologic therapies. This involves analysis of genomic and other biological data in well-phenotyped patients who are commencing a new biologic therapy. It is now clear that due to the complex and multifactorial nature of the disease, multi-omic data is the key to effectively stratify patients and guide systemic therapy accordingly. Another limiting factor is the great expense associated with biologics. Biosimilar drugs which are similar but not identical to established biologics, have now become available as the originator drugs have come off patent. These should reduce the cost of therapy, and so hopefully make biologics more accessible for more patients. It is important to consider the true burden of psoriasis in any health economic evaluation. Direct costs such as medications and hospital appointments are well characterised. Indirect costs such as lost productivity can be more difficult to assess accurately. It has been estimated that indirect costs account for 43% of the mean annual cost of psoriasis amongst those with moderate-

severe disease (103). Some of this could be offset by timely and effective treatment. Psoriasis patients with comorbidities use more healthcare resources and generate higher costs compared to those without comorbidities (104). Screening for and more aggressive treatment of such comorbidities may lead to better patient outcomes. Further research is needed in this field to establish the true burden of disease and relative cost effectiveness of therapy.

Although there are lots of therapies licensed for psoriasis, access to appropriate care remains a problem for many patients around the world. These inequalities are highlighted by the World Health Organisation in their Global Report on Psoriasis (105). The Global Psoriasis Atlas (GPA) aims to address this problem, firstly by establishing the true incidence and prevalence of disease, and then investigating the true burden of disease internationally. This in turn will enable any person with psoriasis, wherever they live in the world, access to the best available care locally.

The biologic revolution has transformed the standard of care for patients with severe disease. However, the majority of patients with psoriasis have mild–moderate disease in terms of cutaneous extent. Unfortunately, there have not been many new therapeutic developments for this group. Topical therapies remain the most commonly prescribed class of drug for psoriasis (106). It is hoped that small molecule therapies which are currently in the pipeline may be accessible for patients with moderate disease.

Randomised controlled trials (RCTs) are the gold standard when it comes to investigating the efficacy and safety of new therapies and most of the evidence which informs clinical guidelines is based on this principle. However, rigorous inclusion and exclusion criteria often mean that the study population is not representative of the usual, real world clinic population. For instance patients with psoriasis identified as being ineligible for RCTs of biologics are at least twice as likely as eligible patients to suffer serious adverse events (107, 108) and reduced efficacy. Prospective longitudinal data collection through pharmacovigilance registers such as The British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) provides an invaluable service to patients and clinicians by providing real-world safety and efficacy data.

Patients with psoriasis accumulate excess physical, psychological and socioeconomic morbidity throughout their lives (4). The reason for this is multifactorial and due to a combination of genetic, behavioural and environmental factors which are unique to an individual. Unfortunately, it is not yet possible to predict which newly diagnosed patient with psoriasis will go on to develop severe disease and associated co-morbidity. The natural history of psoriasis remains poorly understood. It has been suggested that systemic inflammation in psoriasis, perhaps emanating from adipose tissue, contributes to the increased risk of comorbidity (109) and provides further rationale for managing psoriasis with systemic therapies. It has been hypothesised that early intervention with systemic therapy could modify the course of disease and, as a result, reduce the potential for this cumulative impairment which can severely limit a patient from reaching their full potential. Identifying patients at an early stage in their disease course would also provide an opportunity to proactively screen for comorbidities and unhealthy lifestyle behaviours associated with psoriasis, providing an integrated systems approach to management. The collection of multi-omic (genomic, biochemical, demographic, phenotypical, clinical) data from patients with recent-onset disease could provide novel insight into subclinical predictors of disease progression and multi-morbidity (110). Ideally, longitudinal follow up could help determine the characteristics of patients who develop specific disease and comorbidity patterns. Stratification using algrithms based on these multi-omic data is likely to play a key role in guiding the management of immune mediated inflammatory diseases, such as psoriasis, in the future.

CONCLUSION

The evolution of psoriasis treatment over the past 100 years is a celebration of the advances which have been made in understanding and improving care for patients with this disease. A collaborative approach between clinicians, patients, academics and the pharmaceutical industry has been instrumental in enabling this progress. Whilst a cure for psoriasis is unlikely anytime soon, complete clearance of the disease with the newest biologic therapies is now a realistic goal for some. A whole person approach to disease management that embraces the P4 medicine principles of prediction, prevention, personalised therapy and patient participation is the logical extension of our realisation that psoriasis is a "systemic disease" with important physical and psychosocial consequences. Although systemic therapy of psoriasis has advanced considerably there is still an unmet need for more effective topical therapies and a more widespread use of biosimilars.

Future research will focus on the use of integrated multi-omic data to stratify patients and guide therapy. Improved access to care and early intervention with systemic therapy are concepts which are being discussed increasingly. This is where service development overlaps with research, calling for innovative approaches and research methodologies to achieve this goal.

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