

Drug therapies in dermatology

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ABSTRACT

This article explores the current and emerging therapies for skin disease, with a particular focus on chronic plaque psoriasis and metastatic malignant melanoma. We discuss the current biological therapies used for psoriasis and those on the horizon, including small molecules and biosimilars. We also summarise the recent advances in the use of novel therapeutic agents in other dermatological diseases and outline the promise of translational research and stratified medicine approaches in dermatology. Better matching of patients with therapies is anticipated to have a major effect on both clinical practice and the development of new drugs and diagnostics.

KEYWORDS: Psoriasis, biological therapies, tumour necrosis factor antagonists, atopic dermatitis, malignant melanoma

Chronic plaque psoriasis

Psoriasis is a chronic inflammatory skin disease characterised by various clinical forms, with chronic plaque psoriasis being the most common (Fig 1). It affects 1–3% of the population worldwide, causes significant morbidity and diminishes quality of life through adverse effects on physical and emotional well-being.¹

An aberrant T cell-mediated immune response is crucial in the development of chronic plaque psoriasis, which is characterised by extensive inflammation and altered epidermal keratinocyte proliferation and differentiation.^{2,3} It is a prototypic T helper (Th) 17 disease and cytokines, including tumour necrosis factor (TNF)- α , interleukin (IL)-23, IL-21, IL-22 and IL-17, are highly upregulated in involved skin.⁴ Conventional systemic therapies for plaque psoriasis, such as ciclosporin, methotrexate, acitretin and fumaric acid esters, are insufficient to meet the long-term needs of patients with severe disease.⁵

Current biological therapies in dermatology

In the UK, there are four biological agents approved by the National Institute for Health and Care Excellence (NICE) for the treatment of chronic plaque psoriasis.⁶ These are the TNF- α antagonists etanercept, adalimumab and infliximab, and the



Fig 1. Severe chronic plaque psoriasis.

anti-IL12/23 agent, ustekinumab. Biological agents for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and management of psoriasis. Adalimumab, etanercept and ustekinumab are recommended as a treatment option for adults with plaque psoriasis when the following criteria are met: (i) the disease is severe, as defined by a Psoriasis Area and Severity Index (PASI) score of 10 or more and a Dermatology Life Quality Index (DLQI) score of more than 10; and (ii) psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and psoralen ultraviolet A (PUVA), or the patient is intolerant of, or has a contraindication to, these treatments. Infliximab has similar indications, except the PASI score must be 20 or more and the DLQI score greater than 18.

Tumour necrosis factor antagonists

TNF- α is a key proinflammatory cytokine in the pathogenesis of psoriasis that is released from a variety of cells, including T cells and keratinocytes. It is released as a soluble cytokine (sTNF) following cleavage from its cell surface-bound precursor (tmTNF). Both sTNF and tmTNF act by binding TNF receptor 1 (TNFR1, p55) and TNF receptor 2 (TNFR2, p75), leading to nuclear factor (NF)- κ B activation, which promotes keratinocyte proliferation and/or inhibition of keratinocyte apoptosis.⁷ Etanercept, adalimumab and infliximab are the three main

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TNF- α antagonists commonly used in dermatology and data from high-quality randomised controlled trials indicate that all three are highly effective for the management of chronic plaque psoriasis.

Etanercept

As a recombinant human TNF- α receptor protein (p75) fused with the Fc portion of immunoglobulin (Ig)G1, etanercept binds both soluble and membrane-bound TNF- α .⁸ It is given as a 25-mg, twice-weekly subcutaneous injection and its onset of action is slower compared with adalimumab or infliximab, with significant improvement apparent between 4 to 8 weeks after initiation. Thirty-four percent of patients achieved a 75% improvement in clinical severity (PASI 75) by week 12 with this dosage of etanercept; however, there are no trial data on the efficacy of increasing the dose to 50 mg twice weekly in those patients who fail to respond to 25 mg twice weekly.⁹ The PASI 75 is the gold standard primary outcome for trials of therapies in severe psoriasis.

Adalimumab

Adalimumab is a fully humanised monoclonal antibody that binds soluble and membrane-bound TNF- α . It is effective in controlling psoriasis and associated psoriatic arthritis. Adalimumab is recommended as an 80-mg subcutaneous injection at week 0, 40 mg at week 1, and then 40 mg at alternate weeks thereafter. Rapid improvements can be seen within 2 weeks of treatment and maximal disease response is achieved between weeks 12 and 16. A phase III clinical trial demonstrated a PASI 75 of 71% at 16 weeks for patients treated with adalimumab.¹⁰

Infliximab

Infliximab is a chimeric antibody of murine and human constituents that avidly binds soluble, membrane-bound and trans-membrane TNF- α . It is recommended for use as a 5 mg/kg intravenous infusion at weeks 0, 2, 6 and then every 8 weeks. Evidence shows that it is highly effective for both psoriasis and nail psoriasis, with a rapid onset of action; 79% of patients achieved a PASI 75 response by week 10.¹¹

Adverse effects

The most common adverse effects of TNF- α antagonists include upper respiratory tract infections, headaches, sinusitis and injection site reactions. A small increased risk of skin and respiratory infections in addition to non-melanoma skin cancer has been reported. Patients with a personal or family history of demyelinating disorders or heart failure (New York Heart Association class III or IV) should not be treated with TNF- α antagonists. Given that these drugs are immunosuppressive, they should be avoided in individuals with a personal or strong family history of malignancy. They can also reactivate latent tuberculosis and guidelines recommend screening those at risk.

Anti-interleukin-12 and interleukin-23 biological therapy

Both IL-12 and IL-23 are highly expressed in involved skin in psoriasis.¹² IL-12 is a heterodimeric cytokine produced by

dendritic cells, Langerhans cells, B lymphocytes and phagocytic cells.¹³ It promotes the differentiation of naïve T cells into Th1 cells and stimulates production of other proinflammatory cytokines, including interferon (IFN) - γ and TNF- α by T lymphocytes and natural killer (NK) cells. IL-23 is produced by activated macrophages and dendritic cells and is an important regulator of Th-17 lymphocyte proliferation and activity. Cytokines produced from these lymphocytes form a pathway, often referred to as the 'IL-23 pathway' or the 'IL-23/17 pathway', which contributes significantly to the pathogenesis of psoriasis.

Ustekinumab

Ustekinumab is a fully human, monoclonal antibody that blocks the activity of p40, a protein subunit shared by IL-12 and IL-23, and is currently approved for the treatment of moderate to severe psoriasis. The recommended dose for plaque psoriasis is 45 mg for patients weighing <100 kg or 90 mg for patients weighing \geq 100 kg, administered at weeks 0 and 4 and then every 12 weeks thereafter.¹⁴ PHOENIX I and II were phase III clinical trials for ustekinumab that demonstrated that 66.7–67.4% and 66.4–75.7% of patients achieved a PASI 75 after 12 weeks with either 45 mg or 90 mg, respectively given at weeks 0 and 4.¹⁵

Biological therapies have provided a significant advance in the management of severe psoriasis. However, off-label uses in skin conditions have increased considerably, with promising results for recalcitrant diseases, such as pyoderma gangrenosum and hidradenitis suppurativa.

Future biological therapies in dermatology

Interleukin-17 inhibitors

The proinflammatory cytokine IL-17A, a product of Th17 cells (a class of helper Th cells that acts outside the established Th1/Th2 paradigm for the regulation of innate and adaptive immunity)¹⁶ is increased in plaques of psoriasis and is recognised to have a crucial role in the disease.¹⁷ In psoriasis, IL-23 induces T cell production of IL-17A in the skin, which leads to disease progression.¹⁶ Therefore, blocking the action of IL-17 would appear to be favourable in the treatment of this disease.

Secukinumab

Secukinumab is a fully human IgG1 κ monoclonal antibody that selectively binds and neutralises IL-17A. In 2012, a phase II regimen-finding study of subcutaneously administered secukinumab induction and maintenance therapy showed significant efficacy for the treatment and was well tolerated in patients with moderate to severe plaque psoriasis.¹⁸ A similar investigational study showed that treatment with subcutaneous secukinumab produced significantly higher rates of PASI 75 vs placebo and again was well tolerated in patients with moderate to severe plaque psoriasis.¹⁹ However, the PASI 90 response rate vs placebo after 12 weeks of treatment was statistically significant only in the 2 \times 150 mg group.

Ixekizumab

Ixekizumab is a humanised IgG4 monoclonal antibody that neutralises IL-17A. In one of the first phase II studies, Leonardi *et al*²⁰ assessed the efficacy and safety of ixekizumab for the

treatment of moderate to severe plaque psoriasis. Their results at 12 weeks showed significant reduction in the PASI score by at least 75% (25 mg (76.7%), 75 mg (82.8%) and 150 mg (82.1%) and demonstrated efficacy for the difficult-to-treat areas, such as the scalp and nails. Seventy-one percent of patients receiving the higher dose of 150 mg achieved a PASI 90 and 39.3% a PASI 100.

Brodalumab

Brodalumab is a human, anti-IL-17R monoclonal antibody that antagonises the IL-17 pathway. It binds with high affinity to human IL-17RA and blocks the biological activity of interleukins 17A, 17F, 17A/F heterodimer and 17E.²¹ Papp *et al*²² were the first to assess the efficacy and safety of brodalumab for the treatment of patients with moderate to severe plaque psoriasis. Their results showed a mean improvement in the PASI score of approximately 85% at week 12 for patients receiving either 140 mg or 210 mg brodalumab. In those receiving 210 mg, 82% achieved a PASI 75, 75% PASI 90 and 62% PASI 100.

Small molecules

Major disadvantages of biological therapies are that they have to be delivered either subcutaneously or intravenously and are expensive. Therefore, there is a significant need for more cost-effective, orally administered drugs that modulate proinflammatory cytokines. Thus, small-molecular-weight inhibitors (compounds with a molecular weight of less than 1 kDa) have been explored for their potential to treat inflammatory diseases.

Tofacitinib

Tofacitinib is a novel, oral Janus kinase (JAK) receptor inhibitor that is under investigation in plaque psoriasis. Inhibition of JAK1 and JAK3 blocks signalling through the common γ chain-containing receptors for cytokines including IL-2, -4, -7, -9, -15 and -21, which are integral to lymphocyte function. Inhibition of these signalling pathways results in the modulation of certain aspects of the immune system.²³ Papp *et al*²⁴ recently published the results of their phase IIb study investigating the efficacy and safety of tofacitinib vs placebo in patients with moderate to severe chronic plaque psoriasis. The study demonstrated the importance of the JAK pathway in the pathogenesis of plaque psoriasis. Although the sample size was small and treatment duration was short, at week 12, PASI 75 response rates were 25% (2 mg twice daily), 40.8% (4 mg twice daily) and 66.7% (15 mg twice daily), compared with placebo and it was generally well tolerated. The drug is currently in phase III trials.

Another oral JAK1/2 inhibitor, baricitinib, is currently being evaluated in a phase IIb trial for moderate to severe psoriasis and the preliminary results are expected later in 2014.²⁵

Apremilast

Although research for oral treatments has largely been dominated by kinase targets, other small molecules are in development, including those designed to inhibit

phosphodiesterase (PD) E4. Phosphodiesterases uniquely hydrolyse and degrade cyclic adenosine monophosphate (cAMP) and, of the 11 subtypes, PDE4 is widely expressed in many cells, including keratinocytes. Many of the cytokine mediators of psoriasis are influenced by PDE4 activity and a recent study demonstrated the potential of apremilast, a novel orally available small molecule that specifically targets PDE4, to restrict TNF- α production from keratinocytes and NK cells, the major constituents of psoriatic skin lesions.²⁶ Two large phase II trials investigating the effectiveness of apremilast in the treatment of psoriasis, involving more than 600 patients, demonstrated PASI 75 response rates of 11% (10 mg twice daily), 29% (20 mg twice daily) and 41% (30 mg twice daily) in patients treated with apremilast compared with a 6% response rate in the placebo group.^{27,28}

The ongoing phase III trials will facilitate a thorough determination of whether the efficacy outweighs the adverse event profile (headaches, nausea, nasopharyngitis and diarrhoea) to qualify apremilast to be the first PDE4 inhibitor licensed for the treatment of psoriasis. The key trials will be those that compare the newer small molecules directly with traditional systemic therapies, such as methotrexate, and with biological therapies. An ongoing phase III trial is directly comparing apremilast with etanercept for psoriasis.²⁹ Table 1 summarises the current and future biological therapies for the treatment of psoriasis.

Table 1. Summary of current and future biological therapies for the treatment of moderate to severe chronic plaque psoriasis.

Name (brand name)	Manufacturer	Type	Target	Phase of development
Etanercept (Embrel)	Wyeth (formerly Pfizer)	Biologic	TNF- α	Approved 2004
Infliximab (Remicade)	MSD	Biologic	TNF- α	Approved 2006
Adalimumab (Humira)	Abbott	Biologic	TNF- α	Approved 2008
Ustekinumab (Stelara)	Janssen-Cilag	Biologic	IL-12/IL-23	Approved 2009
Secukinumab	Novartis	Biologic	IL-17	Phase III
Ixekizumab	Eli Lilly	Biologic	IL-17	Phase III
Brodalumab	Amgen	Biologic	IL-17 receptor	Phase III
Apremilast	Celgene	Small molecule (oral)	PDE4	Phase III
Tofacitinib	Pfizer	Small molecule (oral)	JAK	Phase III

IL = interleukin; JAK = janus kinase; PDE4 = phosphodiesterase type 4; TNF = tumour necrosis factor.

Biopharmaceuticals and biosimilars

Biological therapies comprise complex polymers of amino acids that vary in size and sequence. Each step of the manufacturing process of biosimilars provides an opportunity to change their characteristics relative to the original.

The TNF- α antagonists (eg etanercept, adalimumab and infliximab) are the most commonly used biological agents for the treatment of moderate to severe psoriasis. Although all three drugs target TNF- α , the process of manufacturing for each drug differs and this feature can impact the relative affinity for TNF- α , the reversibility and/or irreversibility of binding, dosing mode (intravenous vs subcutaneous), dosing intervals and immunogenicity of each drug.^{30,31} The European patent for etanercept will expire in February 2015 and, as a result of the potential revenue, it is likely to stimulate the introduction of biosimilar copies with companies already actively pursuing etanercept biosimilars. The introduction of biosimilars to dermatology could, if priced appropriately, provide substantial financial benefit and could create a means to benefit patients with psoriasis in developing countries. However, biosimilars will be inherently different from the innovator products and, if they are substituted, it should be done so with rigorous therapeutic rationale and be considered as a change in the clinical treatment of the patient.

Atopic dermatitis

Atopic dermatitis (AD) is the most common inflammatory skin disease, affecting up to one in four children and up to 3% of the adult population; together with asthma and allergic rhinitis, it constitutes the triad of atopy.³² Specific therapies for AD are limited and conventional and the most commonly used are not based on a scientific understanding of the disease. The discovery that null mutations in the gene encoding filaggrin are associated with AD represents the single most significant breakthrough in understanding the genetic basis of this complex disease. Filaggrin has a key role in epidermal barrier function, and association of mutations with AD emphasises the importance of barrier dysfunction in the pathogenesis of the disease. Translation of understanding the functional relevance of mutations on filaggrin offers real potential for future therapies in AD. Feasibility studies are currently underway to investigate the therapeutic potential of barrier enhancement using emollients and experimental evidence is emerging to show that the gene encoding filaggrin is amenable to upregulation.³³

AD, in contrast to psoriasis, currently lacks any effective biological treatment and a clearer understanding of the key functional mechanisms in atopy will be required to identify appropriate targeted biological agents. In the meantime, there is an opportunity to focus on barrier improvement with bespoke emollients and/or filaggrin replacement.

Chronic idiopathic urticaria

Chronic idiopathic urticaria (CIU) has a non-specific cause characterised by the spontaneous emergence of wheals and/or angioedema without external physical stimuli. Current guidelines recommend a stepwise approach to treatment, beginning with non-sedating antihistamines, increasing the dose four-fold if symptoms persist, and then to consider

ciclosporin, H2 antagonists, dapsone or omalizumab. Omalizumab is a recombinant monoclonal antibody currently approved for treatment of moderate to severe persistent asthma and works by blocking the binding of IgE to the Fc ϵ RI receptor on the surface of target cells, including mast cells, thereby reducing the release of inflammatory mediators. Although limited by small sample size, a recent phase II study investigating the efficacy and safety of omalizumab in patients with CIU demonstrated that a fixed dose of 300 or 600 mg of omalizumab provided rapid and effective treatment in those patients who were symptomatic despite treatment with antihistamines.³⁴

Metastatic malignant melanoma

The incidence of cutaneous malignant melanoma is increasing more than any other type of cancer and metastatic melanoma is the most aggressive form of skin cancer, with approximately 2,200 annual deaths in the UK and 46,000 worldwide.³⁵ Before 2011, dacarbazine and high-dose IL-2 (HD IL-2) were the only two US Food and Drug Administration (FDA)-licensed therapies for metastatic melanoma. However, both agents were limited by low response rates and severe multiorgan toxicity.

Approximately half of all patients with cutaneous melanoma have an activating mutation in a gene encoding the serine/threonine kinase protein kinase v-RAF murine sarcoma viral oncogene homolog B1 (BRAF).³⁶ In 90% of cases, this activating mutation results in substitution of glutamic acid for valine at amino acid 600 (V600E mutation), with most of the remaining 10% comprising alternate substitution at the V600 locus.³⁷ Mutated BRAF leads to the activation of the mitogen-activated protein kinase (MAPK) pathway, which increases cellular proliferation and drives oncogenic activity.

Vemurafenib

Vemurafenib is a highly selective inhibitor of the kinase domain of mutant BRAF (V600E) that has no effect on wild-type BRAF. Initial trials showed that vemurafenib had a high level of activity in patients with advanced melanoma containing the V600E BRAF mutation and these results were confirmed in the BRIM-3 trials, which compared vemurafenib with dacarbazine in 675 previously untreated patients with either metastatic disease (95%) or unresectable stage IIIC disease (5%).³⁸ The results showed significant improvements in the overall survival (estimated 6-month survival rates: 84% vs 64%, respectively) and progression-free survival (median: 5.3 vs 1.6 months, respectively) as well as significant improvements in response rates (48% vs 6%, respectively).³⁹ The most common adverse effects related to vemurafenib were arthralgia, fatigue, deranged liver function tests and cutaneous complications, such as photosensitivity, accelerated growth of squamous cell carcinomas (SCC) and keratoacanthomas, and skin papillomas. SCCs occur through paradoxical activation of MAPK signalling that bypasses the inhibition of BRAF in precancerous keratinocytes that carry oncogenic mutations in RAS genes.⁴⁰ Vemurafenib was approved by the FDA in August 2011 for use in patients with melanomas containing the V600E BRAF mutation. Dabrafenib is another selective BRAF inhibitor in development.⁴¹

Ipilimumab

Melanoma is an immunogenic tumour characterised by the presence of tumour-infiltrating lymphocytes, occasional spontaneous regression and clinical response to immune stimulation. The CTLA-4 receptor on T lymphocytes is a negative co-stimulatory (requiring the presence of the B7 molecule) regulator of T cell activation that has greater avidity for B7 on antigen-presenting cells than does CD28. Ipilimumab is a fully human IgG1 monoclonal antibody that blocks CTLA-4. Two phase III randomised clinical trials have evaluated ipilimumab in metastatic melanoma in both previously untreated and previously treated patients, each demonstrating significant durable benefits in metastatic or unresectable melanoma.^{42,43} The average overall survival from both studies was 10.6 months, although the response rate and disease control rate were approximately 10% and 30%, respectively. Fig 2 shows a CT scan of abdomen of a 59-year-old patient with stage IV melanoma, highlighting in 4.9 × 3.8-cm conglomerate right external iliac nodal metastases before (a) and (b) after three cycles of ipilimumab, showing complete resolution. There are ongoing studies to ascertain whether higher dosing regimens and combination therapies increase the clinical benefit of ipilimumab.

Oncological approaches for the treatment of non-melanoma skin cancer

Dermatology is embracing change as the management of non-melanoma skin cancer (NMSC), which includes basal cell carcinoma and SCC, is starting to shift from surgery to medical management in line with other branches of cancer treatment.

Vismodegib

Basal cell carcinoma (BCC) is the most common cancer in the UK and its incidence is increasing. Current treatment modalities include surgical excision, radiotherapy, photodynamic therapy and topical agents, such as 5-fluorouracil and imiquimod. However, locally advanced BCCs cannot be surgically excised or treated with radiotherapy without causing some degree of functional and cosmetic impairment. Studies involving the embryogenesis of *Drosophila melanogaster* led to the discovery of the Hedgehog signalling pathway, which is intrinsically involved in embryonic growth, signalling and development. It is quiescent in adult tissues with the exception of hair, skin and stem cells. Unchecked activation of the Hedgehog pathway is present in most BCCs, resulting in unregulated proliferation of basal cells. The important mutation identified in BCCs is the loss of function of patched 1 (*PTCH1*), a tumour suppressor gene, resulting in a failure to inhibit a seven transmembrane protein, smoothened homologue (SMO)⁴⁴. Vismodegib, a Hedgehog pathway inhibitor, has recently been licensed by the FDA for the treatment of advanced BCC. Phase II trials have demonstrated efficacy but adverse effects are frequent and include weight loss, fatigue, alopecia and myalgia. Alternative Hedgehog pathway inhibitors are currently in clinical development.

Ingenol mebutate

Actinic keratoses are premalignant skin lesions that are common in light-skinned populations worldwide.⁴⁵ Commonly used

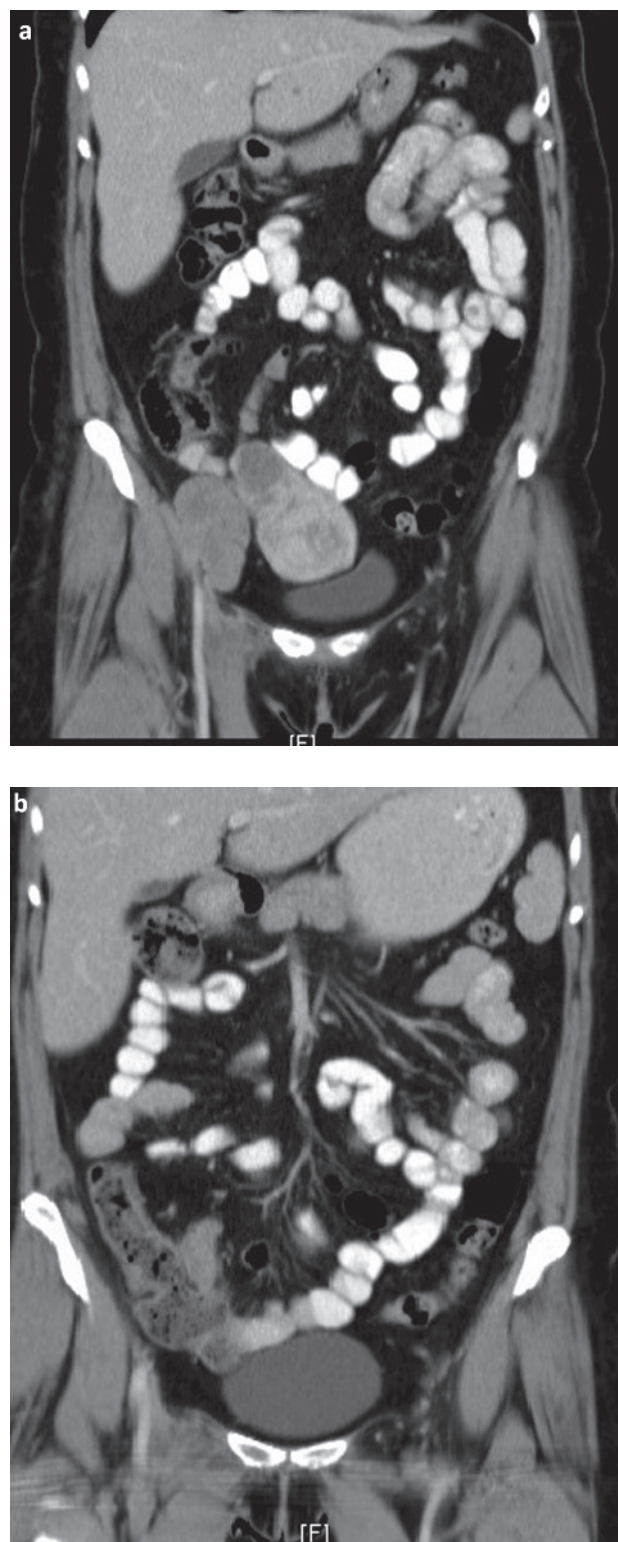


Fig 2. Treatment of malignant melanoma with ipilimumab. (a) Abdominal CT scan showing large right external iliac nodal metastases before (b) after three cycles of ipilimumab therapy. CT = computed tomography.

topical field therapies include diclofenac, fluorouracil and imiquimod, but these require a long duration of treatment and high rate of local reactions that can impair adherence. Ingenol mebutate is a macrocyclic diterpine ester derived from *Euphorbia plepus* that has long been used as a traditional remedy for common skin lesions, including cancerous lesions. A recent randomised controlled trial showed that 42.2% of patients had complete clearance of actinic keratoses on the face and scalp at day 57 of treatment compared with 3.7% of patients in the placebo group. It is marginally less effective in comparison (34.1%) when used on the trunk and extremities.⁴⁶

Propranolol for infantile haemangiomas

A recent serendipitous development in paediatric dermatology is the treatment of infantile haemangiomas (IH) with propranolol. Haemangiomas are the most common benign tumours of infancy and, although most eventually undergo spontaneous resolution, they can still cause disfigurement and serious complications depending on their location and size. Standard treatment options for complicated haemangiomas previously included oral corticosteroids, laser surgery, vincristine or interferon. However, in 2008, Léauté-Labrèze *et al*⁴⁷ described their landmark discovery of the effectiveness of oral propranolol for two children with infantile haemangiomas who were treated with propranolol for cardiac reasons. Although the precise mechanism of action has not been elucidated, propranolol has become the first-choice therapy for complicated infantile haemangiomas.

Potential for stratified medicine

Current prescribing practice is 'trial and error' rather than targeted to the individual patient, thereby resulting in suboptimal responses. Advances in understanding mechanisms underlying diseases as well as drug responses are increasingly creating opportunities to match individual patients with therapies, thereby increasing both their effectiveness and safety. Stratified medicine is already commonplace in oncology, where a companion diagnostic is used to identify optimal responders to a drug pretreatment (eg epidermal growth factor receptor expression and Herceptin for breast cancer). Pretreatment stratifiers can range from clinical phenotype to genotype or, more commonly, a mix of biomarkers, the so-called 'endotype'. Stratified medicine adds another step to traditional clinical practice. After the diagnosis is made on the basis of history, examination and diagnostic tests, stratified medicine adds a clinical biomarker assessment step to associate a patient with a specific therapy. Stratification is not limited to new therapies, but could enable safer and more effective use of older therapies, such as methotrexate.

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