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Psoriasis: TNF-α inhibitors and beyond

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Psoriasis is an uncomfortable, often painful, disfiguring dermatological condition caused by the non-malignant over-proliferation of keratinocytes. It is rarely life-threatening but is undeniably life-ruining to many of the estimated 14 million sufferers worldwide. An estimated 25% of sufferers have contemplated suicide as a result of having to suffer with the disease itself and also the social stigma of such visible, unsightly symptoms.

The psoriasis spectrum

Psoriasis has many manifestations. The most common type is chronic plaque psoriasis, which accounts for 80% of cases and presents as raised red patches of skin with silvery scales. It occurs when T-lymphocytes at the surface of the skin become activated in error, producing inflammatory cytokines that stimulate keratinocytes to proliferate at up to seven times their normal growth rate. These extra skin cells cannot be shed quickly enough and build up, forming plaques. The plaques derive their colour from trapped red blood cells.

Disease severity is measured by body surface coverage; the palm of one hand represents 1% of the body surface. Less than 2% coverage is rated as mild disease, and over 10% coverage is severe disease. Severity also takes into account the areas affected: psoriasis on the palms or soles of feet might only affect a small area, but can seriously impede walking or daily tasks. Fortunately, plaque psoriasis rarely occurs in these areas, and is typically found on the torso, limbs and scalp. In addition, up to 30% of sufferers will develop joint involvement (psoriatic arthritis), often in their thirties or forties.

Psoriasis was recognized as an autoimmune disease after the discovery of T-cell involvement, but the factors that trigger the disorder are varied and unpredictable. At least a dozen separate chromosomal loci have been implicated, but the strongest causative factors are thought to be environmental. For example, in Europe and the USA, if one identical twin develops psoriasis, the other has a 60–70% chance of affliction, compared with a probability of 20–30% in fraternal twins – suggesting a genetic basis. However, in Australia, the chance of both identical twins developing the disease is only 30%. This phenomenon could be a consequence of the structure of the Antipodean gene pool, or the

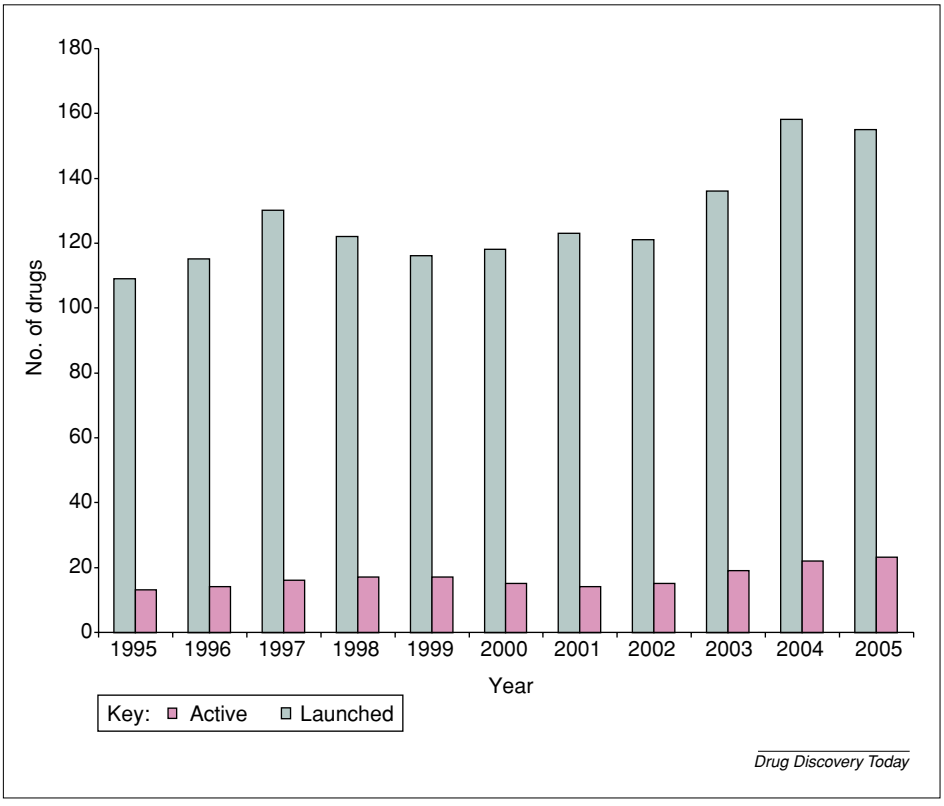

FIGURE 1
Antipsoriatic development trends 1995–2005.

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advantages conferred by its hot, dry climate. This type of weather is known to be beneficial to sufferers, but there are other factors that could have a more detrimental effect.

Streptococcal throat infections have been linked to guttate psoriasis, a form of the disease associated with small skin changes on the torso. Various medications [e.g. antimalarials, β-blockers, steroids and nonsteroidal anti-inflammatory drugs (NSAIDs)] can induce or aggravate flare-ups, as can stress, diet, alcohol and smoking. With seeming irony, steroids and NSAIDs are commonly used as psoriasis treatments. Awareness of environmental factors cannot help patients avoid flare-ups but can reduce the severity of a breakout.

Complex therapeutic options

Psoriasis is currently incurable, but there are many treatments available that can calm the inflamed areas. Unfortunately, the skin often becomes resistant or side effects occur, so each sufferer could use several strategies and drug combinations to maximize response. Side-effects can be severe and include immunosuppression, photosensitivity, increased risks of skin cancer and renal or hepatic toxicity; furthermore, some medications are known to cause rebound flare-ups if treatment is stopped abruptly. Therefore, new prescribing strategies and novel therapies have the potential to revolutionize the safety and efficacy of treatments, and with sales of antipsoriatics expected to exceed US$2 billion by 2007, new generation psoriasis treatments are a potential goldmine for drug companies. In a 2002 survey of 23,622 psoriasis patients, 11.3% had refused treatment, predominantly because of safety or efficacy concerns. This leaves patients in dire need of new options. Indeed, in an ongoing Phase III trial of Isotechnika's antipsoriasis calcineurin inhibitor, ISAtx247, the planned patient recruitment numbers were raised because of the high demand for participation.

Data suggest that the growth of research in this area is unstable (Figure 1), because the number of antipsoriatics in active development appears to fluctuate almost randomly from year to year. However, it is also a relatively low interest therapeutic area, with <160 compounds in development or launched (compared with almost 2000 products under development for cancer). The drop in development from 2004–2005 represents only two compounds, one of which is Serono's onercept, a tumour necrosis factor (TNF) inhibitor. A Phase III psoriasis trial with onercept was recently discontinued as a result of two patients developing sepsis (one fatally).

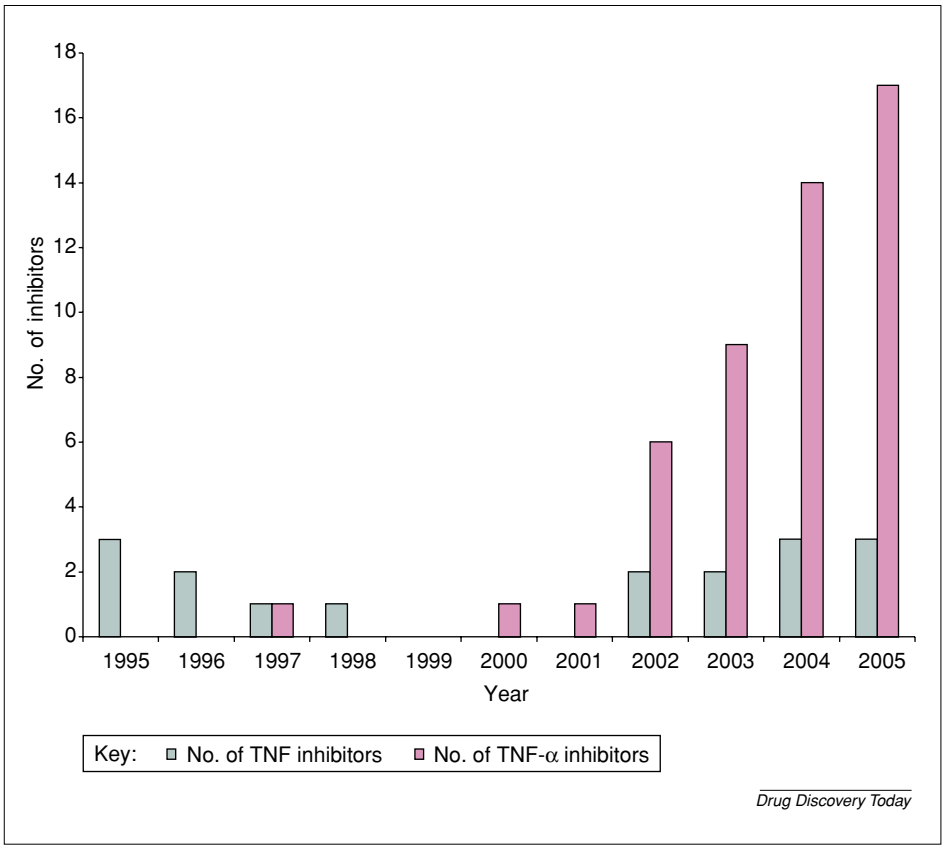

FIGURE 2

Development of tumour necrosis factor and tumour necrosis factor-α inhibitors 1995–2005.

Inhibitors of TNF, in particular TNF-α, have become a popular strategy in recent years. TNF-α is important in the pathogenesis of psoriasis because it induces synthesis of interleukin-1 (IL-1) and IL-8, which cause the inflammation. TNF-α also promotes keratinocyte proliferation and angiogenesis, and thus inhibiting this cytokine should halt the development of the disease at multiple loci. Since 2001, research into TNF-α inhibitors for psoriasis has shown linear growth (Figure 2) and such drugs account for almost 12% of antipsoriatics in development, whereas general TNF inhibitors do not show any clear trends for growth.

Specific inhibition of TNF-α requires synthesis of large, complex molecules; recombinant proteins and monoclonal antibodies are commonly used. These biological medicines tend to be safer than traditional, non-specific agents, because the new, specific immunosuppressives are more targeted, but are not any less synthetic. Unfortunately, they are still mildly immunosuppressive and the risk of sepsis, as seen with onercept, applies to the entire category of drugs. They also demand stringent storage conditions to preserve efficacy, and must usually be administered parenterally. Products of this type include etanercept (launched as Enbrel), a fusion protein that is available for psoriatic arthritis and for psoriasis, and adalimumab (Humira), Abbott's fully human antibody that is in Phase III trials for psoriasis and is awaiting approval for psoriatic arthritis. Centocor's all-purpose autoimmunity treatment infliximab (Remicade) is also in Phase III trials for psoriasis.

ILs present another opportunity to break the disease cycle. Yes Biotech has launched a topical anti-IL-8 antibody product (ABCream) in China after successful trials: psoriasis

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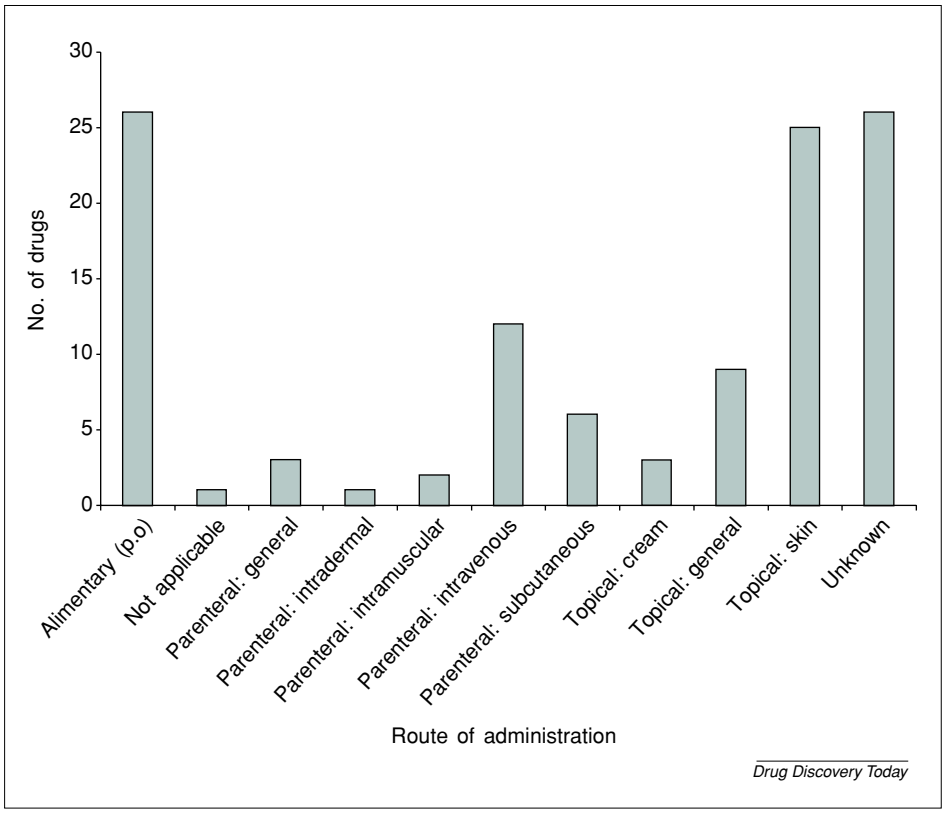

FIGURE 3

Routes of administration of antipsoriatics.

severity was improved by >60% in roughly a half of patients and by >90% in up to 15% of patients. There are many more IL antagonists thought to have potential for psoriasis; drugs with activity against at least seven types of IL, such as IL-6, IL-18 and IL-31, are under investigation (although they are generally in early stages of development). However, these ILs are less crucial components in the aetiology of psoriatic disease, thus compounds targeting them might not prove highly efficacious.

Additional strategies include selectin antagonists designed to stop immune cells reaching the inflamed skin and causing further damage, various conserved domain antigen receptor antagonists to halt T-cell activation and traditional drugs, such as retinoids, optimized with new formulation technologies. The potential for combined or rotational use of assorted new therapies to decrease resistance and toxicity associated with conventional treatment is an exciting thought.

Recent successes

The first biologic treatments to be launched in the USA for severe plaque psoriasis – etanercept and alefacept (Amevive®) – have already demonstrated considerable clinical and financial success. Etanercept sales rose to US$1.9 billion in 2004, an increase of US$500 million on the 2003 figure, because of expanded approval from severe to moderate-to-severe psoriasis. This product is administered subcutaneously, whereas the majority of biological treatments are administered parenterally, because they often degrade rapidly under environmental conditions (meaning that oral and topical preparations are difficult to formulate).

Traditionally, first-line treatment of moderate-to-severe psoriasis consists of topical agents because they are often less invasive than systemic therapy, with a low incidence of the most serious adverse events, such as renal or hepatic failure. Topical products can also soothe and provide immediate relief from symptoms, such as burning and itching – always beneficial in a flare-up. Systemic treatments have been used in more severe, unresponsive cases but new, targeted systemic treatments aim to halt the disease process before symptoms ever appear. The ratio of topical to systemic therapies under development for psoriasis is approximately equal (Figure 3), indicating that new treatments for the full spectrum of disease severity could be under development.

Of the antipsoriatics listed on Pharmaprojects, 57 have specific protein targets. Some of the more novel strategies include Abiogen's preclinical candidate that acts on the melanocyte-stimulating hormone and Antisense Therapeutics' ATL1101, which targets the skin insulin-like growth factor 1: ATL1101 has reached Phase I trials.

The outlook for psoriasis sufferers is improving, with a range of new treatments maturing into safer and all round better products. The number of possible combination regimens also grows with each new launch, further enabling therapy to be tailored to individual needs. The only barrier to successful new medications is the spiralling cost. Perhaps a return to small-molecule drugs will provide the answer? Alternatively, if costs continue to rise, it is not unimaginable that policy makers and insurers will decide not to pay for drugs to treat a non life-threatening condition – a feasible consequence that could leave sufferers itching mad!

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