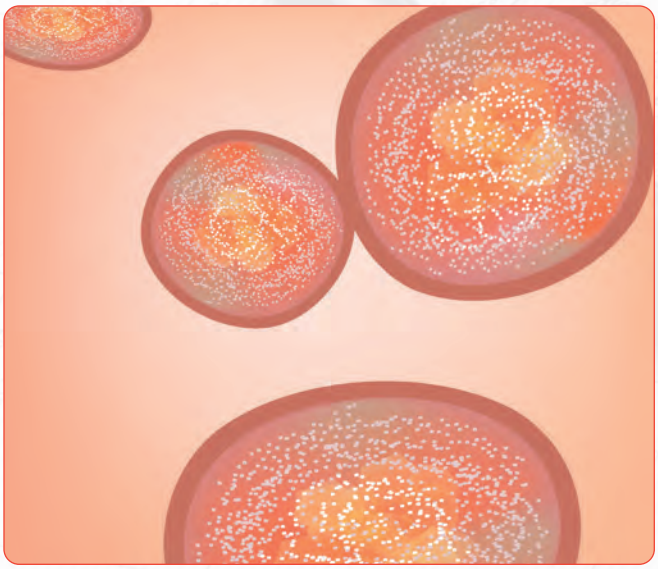
New horizons in treatment

Anyone struggling with a chronic disease wants to know when there is going to be a cure and people living with psoriasis are no exception. Unfortunately, psoriasis is an extremely complex disease and so a cure is still some way off. In the meantime, there is an extraordinary amount of exciting research work going on around the world. Here is a quick digest of some of the most interesting areas currently being investigated – not all of them high-tech!

1. Inflammatory protein targets

Inflammation is the body's natural defence and repair system. If you have an infection or cut yourself, your immune system triggers an inflammatory response, via a special group of proteins called cytokines. Cytokines are special signalling molecules – or 'immunomodulating agents' - which regulate the immune response and inflammation. In psoriasis, this inflammatory response takes on a life of its own and is directed against the body's skin cells, pushing them into overdrive (sometimes referred to as a cytokine storm). In fact, skin cells are made at a rate up to seven times faster than normal, resulting in the plaques, scaling and itching typical of psoriasis.

Examples of pro-inflammatory cytokines include tumour necrosis factor alpha (TNF-alpha) and various interleukins, including IL-8, IL-12, IL-17 and IL-23. Unsurprisingly, drugs which block the actions of these cytokines – biologics - have been therapeutic targets identified by pharma companies for many years.



A drug called ustekinumab (Stelara) has been used to treat psoriasis since 2009. It blocks the effects of two cytokine proteins, IL-12 and IL-23. However, scientists now believe that IL-12 may actually protect skin cells from a different inflammatory protein, IL-17. Attacking IL-12 may therefore not be such a good idea and better results may come from focusing on IL-17 and IL-23 inhibitors. This is where the most recent research has been directed - and the results are very promising.

IL-17 and IL-23 inhibitors

A new injectable drug that blocks the activity of IL-17 proteins was approved in 2016. Ixekizumab (Taltz) was given the green light for treatment of moderate to severe psoriasis after the experience of 80% of people in clinical trials improved when taking it. The drug cleared symptoms for almost half the people who tried it, a success rate which few other psoriasis drugs have been able to match. It joins another IL-17 inhibitor, secukinumab (Cosentyx), which was approved to treat psoriasis in 2015.

Three other drugs on the horizon target IL-23. The injectable IL-23 blocker, guselkumab (Tremfya) improved psoriasis better than the more traditional biologics, such as the TNF-alpha inhibitor adalimumab (Humira). Similar results are expected for the other two IL-23 blockers: risankizumab (Skyrizi) and tildrakizumab (Ilumya).

2. Gene-based gels

TNF-alpha, as we saw above, is one of the important inflammatory cytokines and a key driver of psoriasis. It has traditionally been a target for several drugs used in the management of psoriasis.

Now a different approach has been developed, based on three-dimensional spherical nucleic acid (SNA™) particles. These are essentially microscopic spheres of genetic material (nucleic acid) which prevent the body making TNF-alpha. What is innovative is that the new drug – known as AST-005 - is formulated and applied in the form of a topical gel.

A small trial in Germany, involving 25 patients with chronic plaque psoriasis, evaluated the safety, and tolerability of the gel and found no serious adverse events in any patient.

While larger studies are obviously needed, this is an exciting and innovative approach to delivering biologic agents which can directly target inflammatory cytokines in the skin. An obvious potential advantage is that there are usually fewer and less severe side effects with topically applied treatments, compared with oral medications.

3. Healing genes

Researchers from the University of California have discovered one of the key underlying genetic factors involved in repairing the skin lesions of psoriasis.[1] A gene called grainyhead-like-3 (GRHL3), originally discovered in fruit flies and which is known to be important in wound healing, also helps the body to heal psoriasis skin-lesions.

In support of this, they found that deletion of this gene in mice increased the severity and longevity of the psoriasis-like patches. Researchers are now studying whether people with psoriasis have a genetic change that weakens GRHL3's effects and, if so, whether there is a way to boost its healing powers.

The GRHL3 pathway represents an exciting new target for pharmaceutical products designed to enhance the natural mechanisms of skin healing in psoriasis patients.

4. Healing protein

Researchers at the Stanford University School of Medicine have identified a new molecular target - Rac1 - for potential therapies for psoriasis.

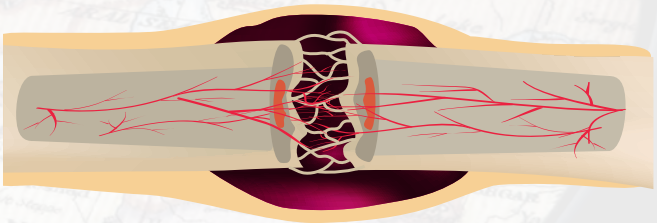
Rac1 is a small protein in the skin which is involved in wound repair. It is also linked to well-known environmental triggers of the disease – such as streptococcal sore throat – which are associated with disease flare-ups. When activated, Rac1 is believed to promote the proliferation of cells in the epidermis, as well as send signals to activate the immune system. Usually this is a necessary and graded response, to promote healing after an injury. But over-proliferation and over-inflammation could have detrimental effects.

Researchers consistently found that Rac1 was highly activated in biopsies of psoriatic skin from 20 people with the condition. When they artificially activated Rac1 in the skin of laboratory mice, the animals exhibited similar symptoms as human patients. They also found that blocking the activity of Rac1 in patches of psoriatic human skin that had been transplanted onto the backs of mice reversed the skin lesions and reduced the concentration of cytokines in the transplanted patch.

As a result, scientists think "switching off" Rac1 may help fight flare-ups. This could lead to treatments that are easier on the immune system than today's biologic drugs.

5. Bone preservation

There is good evidence that patients with psoriasis and psoriatic arthritis have an increased risk of osteoporosis and metabolic bone fracture.[2] The likely mechanism involved is high levels of cytokines, such as TNF-alpha, IL-6 and IL-17. These inflammatory molecules appear to increase bone loss.



A recent study was designed to investigate whether treatment with biologic agents, which inhibit inflammatory cytokines, could help to preserve bone density.[3] This study, which was conducted by researchers in Germany, included 165 patients with psoriatic arthritis (PsA), 34 of whom took methotrexate alone, 52 who used biologics (including adalimumab, infliximab, etanercept, certolizumab, golimumab, secukinumab, and ustekinumab) and 79 who did not take a disease-modifying drug. Those using biologics took the drugs for an average of four years.

Specialised imaging was used to determine bone density and bone microstructure.

Overall, results show that treatment with biologics – but not methotrexate – was associated with significantly better bone structure and function in patients with PsA. The authors conclude that blocking the action of bone-destroying inflammatory cytokines with biologic agents is a key factor in preserving bone health in patients with psoriatic arthritis.

6. Turmeric

Although most natural psoriasis remedies have no scientific research to support their use, a key exception is that of the bright yellow spice turmeric. Its main ingredient, curcumin, can block the protein TNF-alpha, which triggers psoriasis inflammation. Turmeric can be mixed into food or taken as a supplement. But it has also been used in the form of a topically applied gel, with encouraging results.

One trial involving 647 patients with mild to severe psoriasis used curcumin gel, topical steroids, avoidance of contact allergens and avoidance of dairy products for those who were lactose intolerant, as the therapeutic regimen.[4] At 16 weeks follow-up, 72.2% of patients were completely clear of psoriatic activity (PASI = 0). The problem with this trial is obviously that there were several treatments being applied simultaneously, so the specific contribution made by the turmeric gel could not be established.

A better-quality study, using a specially formulated curcumin microemulgel, also showed positive results.[5] This was a placebo-controlled, double-blind, clinical trial of 34 people with plaque psoriasis, who were treated with the microemulgel. The study showed that the microemulgel was well tolerated and that, when compared to those subjects receiving the placebo, participants showed greater improvement in symptoms such as skin redness, itching, thickness and scaling. They also reported an improved quality of life.

Taken together, these studies suggest that various topical formulations of curcumin – while not becoming standalone treatments for psoriasis - may be a useful, low-risk, adjunct therapy.

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