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skin 'n' bones connection

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Dear Reader

Welcome to issue 54 of Skin 'n' Bones Connection.

It is worth reflecting that, although much of life and the news has been dominated by the COVID-19 pandemic and how to defeat it, other important research has continued.

Health-related research takes many forms, but ultimately the aim is to improve the outcomes for real people.

On page 3, a process which started before the pandemic, continued and delivered results, is the priority setting partnership (PSP), with a top-ten list of psoriatic arthritis research priorities has now been published.

The PSP involved real people with lived experience, to aid the outcomes. On pages 6 & 7 you will see how PAPAA uses patients' voices to influence treatment appraisals.

In June, *Patients at the Heart of Innovation* was the theme of the Health Technology Assessment International's annual meeting, reported on page 14 &15. It was held as a virtual meeting, which aided patient involvement, a potential benefit of travel restrictions due to COVID, so perhaps there is light within the darkness.

Starting on page 10 is part two of *A brief history of psoriasis*. The rate that treatments have advanced in recent times is a reflection of the dedication that researchers have and will continue to have, a subject which is highlighted on pages 17, 18 and 19.

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Using digital data to find information. By ARMMY PICCA

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The British Psoriatic Arthritis Consortium (BritPACT) worked with the James Lind Alliance (JLA) to run a priority setting partnership (PSP). They have created a national top 10 list of research priorities for psoriatic arthritis, agreed upon by people with psoriatic arthritis, carers and clinicians. This marks the culmination of the psoriatic arthritis PSP, a process run by the JLA, which we hope will be considered by funders to ensure future psoriatic arthritis research focuses on the areas that matter most to the people in the UK who live with the condition, and those involved in its care and treatment.

The project followed the JLA priority setting partnership method, and began with an open call for psoriatic arthritis stakeholders to submit the questions that they wanted answering about the condition and its treatments.

Nearly one thousand questions were received from people living with the condition, their families, GPs, rheumatologists, allied health professionals, nurses and others. These questions were refined through a rigorous and collaborative process, including a second round of voting and a stakeholder workshop day, to agree on the final top ten.

The Top Ten Psoriatic Arthritis Research Priorities are:

1. What is the best strategy for managing patients with psoriatic arthritis, including non-drug and drug treatments?
2. What factors affect how psoriatic arthritis will progress, the likely severity of the disease in an individual, and whether it will go into remission?
3. Can tests be developed to predict whether a person has or will develop psoriatic arthritis?
4. Is a person with psoriatic arthritis at risk of developing other health conditions? If so, which ones and why?
5. Does treating psoriatic arthritis early (or proactively) reduce the severity of the disease and/or make it more likely to go into remission?
6. What triggers acute exacerbations and flares of psoriatic arthritis symptoms?
7. What is the best way to measure outcomes of treatment in psoriatic arthritis?
8. What are the long-term risks and benefits of medications used for psoriatic arthritis?
9. Why do treatments stop working well against psoriatic arthritis and, when they lose effectiveness, what's the best way to regain control of psoriatic arthritis?
10. What treatments present the most benefit (considering efficacy, tolerability and safety) for the different body tissues involved in psoriatic arthritis, for example, joints, tendons, spine, skin and nails?

The aim of this top 10 is to make sure that health research funders are aware of the issues that matter most to the people who need to use the outcomes of research in their everyday lives.

For more information visit:

James Lind Alliance: www.jla.nihr.ac.uk

BritPACT: www.britpact.org

The psoriatic child

When a child becomes ill, with any condition, it can be distressing not only for the child but for the parents, siblings, relatives and friends. It is natural for a parent to be concerned and even when their child is an adult, that concern continues, particularly when they have a chronic condition.

How common is psoriasis in children?

The heredity factor seems to play a part. About one third of people with psoriasis are able to identify a relative, living or dead, with psoriasis. It is estimated that if one parent has psoriasis that there is a 15% chance that a child will develop the condition. If both parents have psoriasis, this increases to about 75%. Interestingly, if a child develops psoriasis and neither parent is affected there is a 20% chance that a brother or sister will also get psoriasis. This is because the condition is known to skip generations and somewhere there will be a familial link to a relative via either or both parents.

How common is arthritis in children?

As many as 12,000 children in the UK are affected by juvenile idiopathic arthritis (JIA).

There are three main types:

- **Systemic JIA (Still's disease)** accounts for 20% of cases. It starts with a high fever, patchy red rash, enlarged lymph nodes, abdominal pain and weight loss.
- **Oligoarthritis** is the most common type of JIA, accounting for 50% of new diagnoses each year. It is diagnosed when four or fewer joints are affected in the first six months of disease.
- **Polyarticular onset JIA**, also known as polyarthritis, accounts for 25% of new diagnoses and is diagnosed when five or more joints are affected in the first six months of disease. After six months from diagnosis, if five or more joints become affected it is then referred to as polyarticular-course JIA. Polyarthritis can be further divided into rheumatoid factor negative arthritis and rheumatoid factor positive arthritis. Polyarthritis includes those diagnosed with polyarticular JIA, but who then have more joints affected after six months, also known as extended oligoarticular JIA.
- **Juvenile psoriatic arthritis (JPsA)**, accounts for 2-15% of new diagnoses and is diagnosed when there is joint pain association with psoriasis.

Juvenile psoriatic arthritis is sometimes thought of as part of the spectrum of juvenile chronic arthritis summarised above, but others regard it as a separate disease to be distinguished from these, having more in common with reactive arthritis and juvenile ankylosing spondylitis.

The Vancouver criteria for diagnosis of psoriatic arthritis in childhood are a useful guide:

Definite psoriatic arthritis

- Arthritis with three of the four following minor criteria:
  - dactylitis (pink, swollen "sausage" finger or toe)
  - nail pitting or onycholysis (splitting and breaking up of nail)
  - psoriasis-like rash
  - family history of psoriasis in first- or second-degree relatives.

Probable psoriatic arthritis

- Arthritis with two of the four criteria listed

Girls are more likely to be affected than boys. Simultaneous onset of rash and arthritis is rather uncommon. As in the adult variety, the end joints of the fingers are commonly involved. Generally, in juvenile chronic arthritis this does not happen but tendons are often inflamed. The knee seems commonest in children to be affected.

What triggers psoriasis in children?

Symptoms can develop if they are triggered by certain events, most frequently in children and teenagers, often after a throat infection due to streptococcal bacteria. This type of psoriasis is known as guttate psoriasis or raindrop psoriasis, so named because it manifests itself over the body in the form of scaly, droplet-shaped patches. Numerous small, red, scaly patches quickly develop over a wide area of skin, although the palms and the soles are usually not affected. Some people may go on in later life to develop chronic plaque psoriasis.

Early diagnosis of arthritis

If a child develops painful joints and there is a family history of psoriasis - even if the child shows no psoriasis at the time - it is worth mentioning the possibility to the doctor and even more so if any family member has psoriatic arthritis. If doubt remains, a referral to a specialist should be made, ideally a paediatric rheumatologist, but as there are only a few paediatric rheumatologists, a general paediatrician or adult rheumatologist with an interest in the condition should be considered.

Treatments

As with adults, children may need some form of treatment of care and management plan for their psoriasis and/or psoriatic arthritis.

Treating psoriasis in children

Generally, those medications used in children are the same as for adult psoriasis, although there may be dosage differences and some products may not be licensed for use in children.

In general, doctors try to control psoriasis in children with topical treatments because they are the safest. Occasionally they may use UV light or systemic treatments, including biologic therapies. The therapeutic needs of each individual, child or adult, are different. Healthcare providers are in the best position to decide what is the appropriate treatment for a child. They will always come to that decision by weighing up the relative risks and benefits involved in each possible treatment, although it should be a shared decision-making process.

Treating juvenile psoriatic arthritis

As with skin psoriasis, treatments for arthritis in children includes those used in adults, but in different formulations or doses. They include nonsteroidal anti-inflammatory drugs (NSAIDs), injection of steroids directly into the affect joint(s), disease-modifying anti-rheumatic drugs (DMARDS) such as methotrexate, biologic medications, regular exercise and physical therapy to improve and maintain muscle and joint function. The risks and benefits of suggested therapies should also be part of any conversation.

In summary:

Psoriasis treatments have a goal of clear skin, although, for some, near clearance is often acceptable. For juvenile psoriatic arthritis the aim is to reduce joint inflammation, maintain mobility and prevent deformity. Overall, the aim of any treatment and care is for a child to have as normal and active a childhood as possible.

More information:

https://www.papaa.org/learn-about-psoriasis-and psoriatic-arthritis/children/

Providing the patient voice

PAPAA has been involved in the appraisals of new therapies with both the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC). As a stakeholder organisation, PAPAA is invited, along with other professional and patient representative groups, to provide the patient perspective. We feel that it is very important that we do this, to provide the lived experience of those affected by psoriasis and/or psoriatic arthritis.

We are also offered the opportunity to nominate individuals to attend the committee meetings as expert patients. This is in order to answer any questions about the conditions and how the proposed therapies are likely to benefit real people or not.

We not only use the organisation's collective knowledge, but draw on the interactions we have had via our information line, correspondence and through attending events. We also use the information provided via our surveys and submissions made to our '*share your story*' website pages. In the past we have been asked to gather specific information about certain aspects of therapies, and are continually grateful to those who respond to our request for input. The processes of treatment appraisal can often be very drawn out and take some significant time, although there are some steps being taken to speed up the process in order to make new therapies available sooner.

In a recent pilot of a new approach to cost-comparison, NICE approved its first treatment under a fast-track appraisal process. The treatment happened to be for severe plaque psoriasis and is called bimekizumab.

As part of the recovery from the COVID-19 pandemic, NICE has been working hard to find new ways to develop and publish guidance affected by the work programme pause in 2020, while also delivering the planned programme for 2021.

To address this, a new approach to the cost-comparison fast-track appraisal process was piloted in the summer for the review of selected low-risk appraisals. The pilot programme worked by using a subset of the appraisal committee to assess low-risk treatments, comparing them to similar therapies that have already been appraised by NICE. This sub-committee was then able to make a recommendation without requiring a full committee meeting. PAPAA provided initial submissions, which were included in the evidence review process.

After an initial recommendation has been made, the guidance is then considered by the entire committee ahead of its release, and a full meeting can be scheduled if any concerns arise. The pilot process does not impact the standard governance or appeal processes.

Clinical trial evidence shows bimekizumab to be more effective at treating the condition than three comparators, which were all previously approved by NICE. The cost-effectiveness estimates are also in line with what is considered to be an acceptable use of NHS resources, so bimekizumab is recommended. Nearly 18,000 people will be eligible for the treatment.

Meindert Boysen, director of the Centre for Health and Technology Evaluation at NICE, said: *"The urgency of the pandemic led to necessary changes to the way NICE prioritised guidance production throughout 2020. As part of our 2021 review into the health technology evaluation process, we are taking this opportunity to introduce new measures to address the impact of the pandemic, including this pilot programme for a limited fast-tracked process.*

"Although our review is still underway, we are pleased to have been able to pilot this new approach to committee decision making to recommend bimekizumab as a treatment option for severe plaque psoriasis.

"It is our hope that we will continue to be able to follow this new process for eligible low-risk appraisals, and release capacity within our committees and the technology evaluation team."

Victoria Barrett, head of HTA & market access policy at the Association of the British Pharmaceutical Industry, said: *"This new approach to ensure some NICE decisions are made in a more efficient way is good news, especially for the patients that stand to benefit. It is important that NICE and its committees have sufficient capacity to issue timely guidance to the NHS, and this is one way to help, given the success of the pilot exercise."*

As well as bimekizumab for severe psoriasis, PAPAA has also contributed to NICE appraisals for secukinumab, which has been recommended as an option for treating plaque psoriasis in children and young people aged 6 to 17 years, and, for psoriatic arthritis, guselkumab, which received a positive recommendation from NICE and the SMC.

Summary of the NICE recommendations and indications as follows:

Bimekizumab: "...the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and the disease has not responded to other systemic treatments, including ciclosporin, methotrexate and phototherapy, or these options are contraindicated or not tolerated and the company provides the drug according to the commercial arrangement."

Secukinumab: "...the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and the disease has not responded to other systemic treatments, including ciclosporin, methotrexate and phototherapy, or these options are contraindicated or not tolerated and the company provides the drug according to the commercial arrangement."

Guselkumab: "...taken with or without methotrexate, for active psoriatic arthritis when disease-modifying antirheumatic drugs (DMARDs) have not worked well enough, or are not tolerated. It is only for adults who have: had 2 conventional DMARDs and at least 1 biological DMARD, peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and moderate to severe psoriasis."

Source:
NICE – www.nice.org.uk
SMC – www.scottishmedicines.org.uk

Skin appearance survey

More than half of those with skin conditions feel judged by others because of it, according to a new British Skin Foundation (BSF) survey. On top of that, a significant number of people with skin conditions say that it affects their mental health, everyday life and often leaves them feeling embarrassed.

The BSF believes that skin and hair are intrinsic to people's identity, with four in five agreeing that their appearance is important to their general wellbeing. Sadly, one in five are unhappy with their skin and appearance in general, while almost all the people surveyed saying they would welcome more research into skin disease.

Matthew Patey, chief executive officer at the British Skin Foundation, said:

"It's clear from the results of our latest survey that skin and appearance play a huge part in our mental health and happiness. Whilst the skin is the body's largest organ, most people underestimate its importance, dismissing skin issues as simply cosmetic. They wouldn't downplay disease concerning other organs in the body so easily. At the British Skin Foundation, we are working to find cures and treatments for all types of skin disease, including skin cancer. Our survey proves that the public are keen for more research into skin problems, which means we need your support today."

A link between the mind and skin has long been recognised. Professor Andrew Thompson, consultant clinical psychologist and British Skin Foundation spokesperson, said:

"We know from a multitude of studies conducted by myself and other researchers working in this area, that skin disease is associated with higher risk of experiencing psychological distress. Whilst there may be both complicated physiological and psychosocial reasons why skin conditions are linked to feelings of anxiety and depression, the good news is that psychological treatment can help and consequently it's important to seek help as soon as symptoms of depression or anxiety are noticed."

Dr Anjali Mahto, consultant dermatologist and British Skin Foundation spokesperson, agrees:

"Sadly, I don't find these statistics a shock or surprise as this data mirrors very much what many of us see in clinic. We can no longer ignore the growing links between the skin and mind; skin conditions are not simply cosmetic or beauty issues and those who are suffering need to be taken seriously. No one should have to feel alone or suffer in silence. Please consider seeking help from your GP or dermatologist if your skin is impacting your ability to live your life on a daily basis."

Appearance and skin problems in British people

- **83% of people** believe that their appearance is important to their general wellbeing.
- **53% of those with skin disease** feel judged by others due to their skin condition.
- **20% are unhappy** with their skin.
- **18% are unhappy** with their appearance in general.
- **92% of people** surveyed would welcome more research into all types of skin disease, including skin cancer.

Of those with skin conditions now or previously:

- **35% say** that their skin condition affects their mental health.
- **26% agree** that they are often embarrassed by their skin condition.
- **25% said** that having a skin disease affects their everyday life.

About BSF: The British Skin Foundation has been funding skin research for 25 years to help find cures and treatments for a wide range of conditions. Increasingly, the psychological aspects of skin disease are rightly recognised for being just as important as the physical manifestations. To date they have raised more than £16 million to fund more than 400 research projects since 1996.

About the survey: This British Skin Foundation survey was undertaken in June 2021 and answered by 201 British people between 18-99 years old (102 male, 99 female).

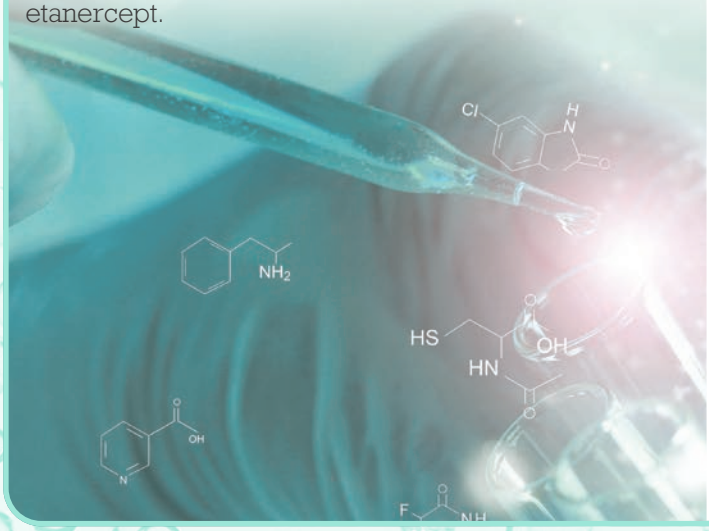
Source:
The British Skin Foundation media release.

The development of a range of biologic treatments over the last decade has revolutionised the management of moderate-severe psoriasis and psoriatic arthritis (PsA). There are various drugs in this category – e.g., sekukinumab, infliximab etc – but they all work by blocking immune system signals involved in the inflammatory process that result in damage to skin and joint tissue.

With the rapid emergence of these new therapeutic agents, evaluating long-term comparative safety is essential, because patients with moderate to severe psoriasis may be at increased risk of infection, depending on the biologic agent used. The purpose of this study was to establish whether there is a significant difference between biologic agents in terms of the risk of serious infection.

The study involved a nationwide French cohort of 44, 239 new users of biologics, followed for a period of 12 months after treatment began. Information regarding serious infection was obtained from hospital records. In all, there were 1656 serious infections, the most frequent being infections of the gastrointestinal system (645 or 38.9%).

There were clear differences in susceptibility to infection, depending on the biologic used. Compared with etanercept, patients taking infliximab and adalimumab were at an increased risk of serious infections. On the other hand, the risk was significantly lower for those on ustekinumab. There was no increase in risk for users of secukinumab, ixekizumab, brodalumab or guselkumab, when compared with etanercept.



Conclusion

This study is an important contribution to the safety profile of biologic therapies. Although more research is needed, these results should help doctors choose a suitable biologic for patients with psoriasis who are at risk of serious infections.

Reference:

Association Between Biologics Use and Risk of Serious Infection in Patients with Psoriasis
Penso L, Dray-Spira R, JAMA Dermatol. 2021;157(9):1056-1065.

Biologic registries

As part of the process of understanding the long-term effects of biologic therapies in people with psoriasis and psoriatic arthritis, there are two registries that gather data in order to provide useful information.

The psoriatic arthritis register is run by the University of Aberdeen on behalf of the British Society for Rheumatology. The register is aligned to other international registries with psoriatic arthritis patients in the EU and North America. The register aims to provide 'real-world' data around:

- the impact of psoriatic arthritis on individuals, including function, work, quality of life and economic impact
- the natural history of psoriatic arthritis, including clinical, social and work outcomes in the medium- to long-term and the impact of disease phenotype on disease outcome.

https://www.rheumatology.org.uk/practice-quality/registers/psoriatic-arthritis

BADBIR is the psoriasis registry and stands for the British Association of Dermatologists Biologic and Immunomodulators Register.

It is a UK and Eire observational study seeking to assess the long-term safety of biologic treatments for psoriasis. The National Institute for Health and Clinical Excellence (NICE) has recommended that all patients in the UK receiving these new therapies for psoriasis should be registered with BADBIR.

http://www.badbir.org

Pathophysiology and treatment

This is the second part of a two-part history of psoriasis. In part one, published in Issue 53, I discussed the evolution in our understanding of the disease, based on the descriptive appearance of psoriatic skin lesions and how these were eventually recognised as representing a disease in its own right.

In part two, I will discuss how our understanding of the underlying disease processes (pathophysiology) has evolved and provide a brief history of the various approaches to treatment over the past 200 years. It is a remarkable story of serendipity and great science.

Pathophysiology

The essential finding in psoriasis is that cells in the epidermis (the outer layer of the skin) multiply up to ten times faster than normal. This process is called epidermal hyperplasia and it results in the thickening, crusting and scaling of the skin so characteristic of psoriasis.

The process of epidermal hyperplasia in psoriatic patients was first observed by E.J. Van Scott in 1963. Three years later, Van Scott and Weinstein noted that skin cells in psoriatic patients rose to the surface in only two days, in contrast to their 12-day transit through normal epidermis. This rapid turnover of epidermal cells was soon shown to be the result of a cascade of autoimmune reactions – meaning that part of the body's immune system becomes overactive and attacks normal tissues. This then results in the release of special inflammatory molecules called cytokines, and the resulting inflammation leads to the characteristic features of psoriasis – reddened, thickened, dry and scaly skin.

Today, we recognise psoriasis to be the result of a complex interaction between immunological, genetic, cellular, and environmental factors. Moreover, numerous studies have unequivocally shown that psoriasis is a systemic inflammatory disease which may have adverse consequences in other organs – including in the heart, liver, kidneys, intestines, muscles and tendons.

The good news is that this rapid development in our scientific understanding of the fundamental mechanisms involved has led to remarkable advances in treatment – to which I now turn.

From arsenic to biologics – a 200-year history of treatments

In 1726, Turner described treating psoriasis with an ointment containing ammoniated mercury or with a broth of boiled vipers. It isn't clear whether any improvement (assuming there was any) was due to the mercury or the boiled viper casserole but (as we will see), in the 19th century both mercury and arsenic were recommended as treatments. These early forms of treatment tended to be internal rather than topical because it was believed that applying medications to skin lesions could drive them inwards and thus affect the internal organs.

19th century – arsenic and ammoniated mercury

Thomas Girdlestone was an English physician and writer who, in 1806, is said to have been the first to advocate the use of arsenical compounds in the treatment of psoriasis – though arsenical compounds had, in fact, been used to treat skin diseases since at least Roman times.

Girdlestone prescribed a solution of 1% potassium arsenite – Fowler's solution – usually given as six drops, three times daily. Other physicians began to recommend the same treatment, which did appear to have some benefit, though mainly in the guttate form of psoriasis. Then, in 1869, Lipp introduced subcutaneous injections of arsenous acid for patients with psoriasis or eczema.

The problem, of course, is that arsenic is one of the most toxic metals derived from the natural environment. It accumulates in the internal organs, causing a range of terrible side effects (which is why it has always been so attractive to the poisoner). It is also a potent carcinogen (cancer-causing agent). Despite this, arsenic preparations remained in use until the middle of the 20th century, when corticosteroids were first introduced.

Mercury was used for centuries in the treatment of skin disease and – notably – syphilis. The great Austrian composer Franz Schubert died from syphilis in 1828 at just 31 years of age. In those days the patient (or perhaps victim) was placed in a sealed room and covered with mercury. They were forbidden to change either their clothing or bed sheets. Patients would complain of abdominal pains, difficulty swallowing, headaches, diarrhoea, and muscle weakness. The doctors explained that these were simply temporary side effects of an effective treatment, but in fact these are all symptoms of chronic mercury poisoning.

Schubert died in Vienna, at the apartment of his brother Ferdinand. He had been unable to eat properly for days and had also become confused. The official cause of death was given as typhus, but this seems unlikely. The more likely explanation is that, although he did have syphilis, it was the treatment rather than the disease that killed him.

For psoriasis, on the other hand, mercury was most often applied as an ointment and remained in use until quite recently. In fact, a letter in the British Medical Journal of 1956 says "mercury ointments are still widely used in the treatment of psoriasis...". As with arsenic, it accumulates in the body and – as we have seen - has potentially serious toxic effects. Interestingly, however, the signatories of the BMJ letter (Inman, Gordon and Trinder), say, "Toxicity due to mercury absorption in the treatment of psoriasis must be rare, and has not been recognised in this clinic". So perhaps in the ointment form, mercury was somewhat less dangerous.

1900-1950 – dithranol (anthralin) and tar

In 1876, Squire inadvertently found dithranol to be an effective treatment for psoriasis. He had prescribed Goa powder, which was until then known only to be effective in ringworm, and the patient's psoriasis improved.

Goa powder is the dried, powdered rubbery sap (latex) from a Brazilian tree called Andira araroba. It turns out that the active ingredient of Goa powder is chrysarobin, also known as 2-methyl dithranol. A synthetic form of dithranol was first produced in 1916 and was then introduced as a therapeutic agent for skin disease by Galewsky.

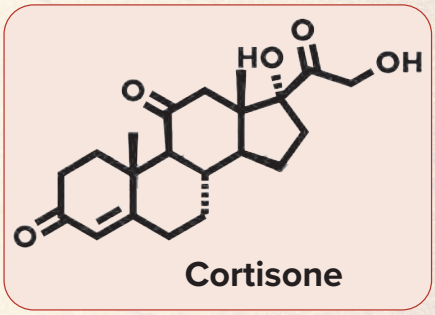
Dithranol was first used in Germany, and later in

Britain, but it has never been popular with American dermatologists, probably due to the side effects of staining and irritation of the skin.

The next big advance in psoriasis treatment was coal tar. Hippocrates and other ancient physicians treated skin conditions with pine tar and other types of tar. Coal tar became available when coal gas production developed in the late 19th century and William Goeckerman – an American dermatologist - found it to be very effective in the treatment of psoriasis. It had an anti-inflammatory action but, unfortunately, it also had an unpleasant odour and some potential for skin irritation. Recognising that summer sun was also helpful in psoriasis, in 1925 Goeckerman showed that a combination of coal tar and UV light was especially effective. Then, in 1953, John Ingram, an English dermatologist, added dithranol paste to UV light and coal tar – known as the Ingram Regimen. Ingram went on to establish the first day-care facility for psoriasis and this general approach remained a cornerstone of psoriasis treatment for decades.

1950s – corticosteroids

In 1950, Hench, Kendall, and Reichstein received the Nobel Prize for the development of cortisone, which heralded the corticosteroid era and a revolution in the treatment of many diseases. Just two years later, cortisone was used as a topical preparation in various skin diseases, though had a limited effect in psoriasis.



Cortisone

However, a variety of synthetic corticosteroids soon followed, which proved to be extremely efficacious in the treatment of psoriasis. There are, however, unwanted effects, including thinning of the skin, and these limit their long-term use.

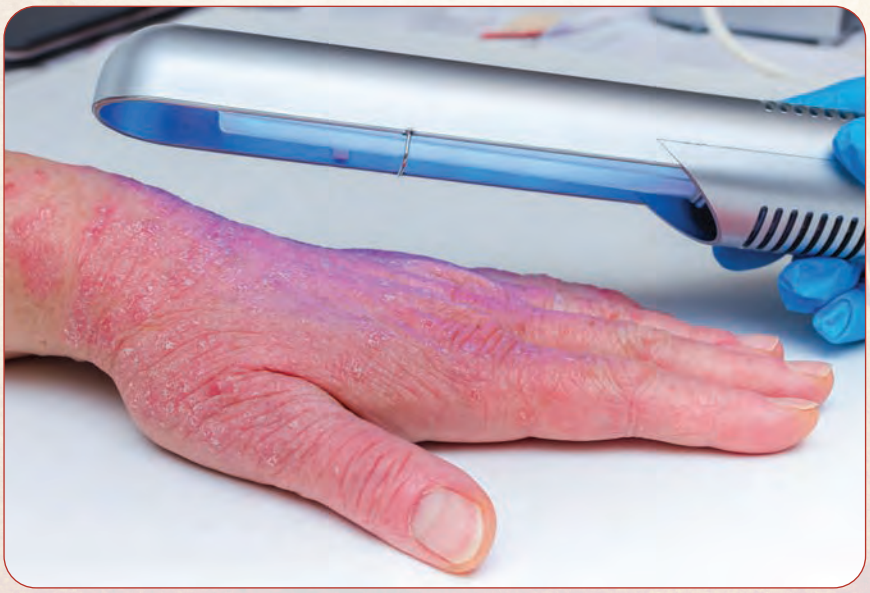
1970s – methotrexate and PUVA

Methotrexate, formerly known as aminopterin, was originally introduced in 1946 as a treatment for leukaemia. Some five years later it was found that aminopterin used in the treatment of rheumatoid arthritis also cleared psoriasis. In 1958, the more stable derivative of aminopterin with lower toxicity – methotrexate – was introduced. In 1972 the drug was approved for use in psoriasis.

Methotrexate works by suppressing the overactive immune system that causes psoriasis. It is a powerful medicine and nowadays is used to treat severe psoriasis and psoriatic arthritis. In most cases, psoriasis is cleared in four to six weeks. Unfortunately, it has several unwanted effects, most notably nausea, headaches and fatigue. It may also cause serious liver damage with long-term use. It is used in the treatment of cancer and various autoimmune diseases, including psoriasis. Methotrexate can be given as tablets, oral solution or by injection.

Another development of the 1970s was PUVA (psoralen and ultraviolet A) therapy, in which the patient is first given a psoralen (a drug containing chemicals that react with ultraviolet light) and then exposed to UVA light. Remarkably, it seems that this idea was known to the ancient Egyptians of around 1500 BC, who used a combination of sunlight and ingestion of plants known as psoralens – including limes and figs – to treat vitiligo (a loss of skin pigmentation).

In 1974 and 1977, the first trials of PUVA in the treatment of psoriasis showed that patients experienced clearing of their skin lesions. Nowadays it is used in the treatment of moderate to severe plaque psoriasis that has failed to respond to topical treatments. Although often therapeutically successful, PUVA therapy increases the risk of skin cancer and may also cause skin damage and premature ageing (all of which also occur with natural sunlight). For this reason, there are specific guidelines as to the total number of UV treatments an individual can have in a lifetime.



1990s – ciclosporin (or cyclosporine)

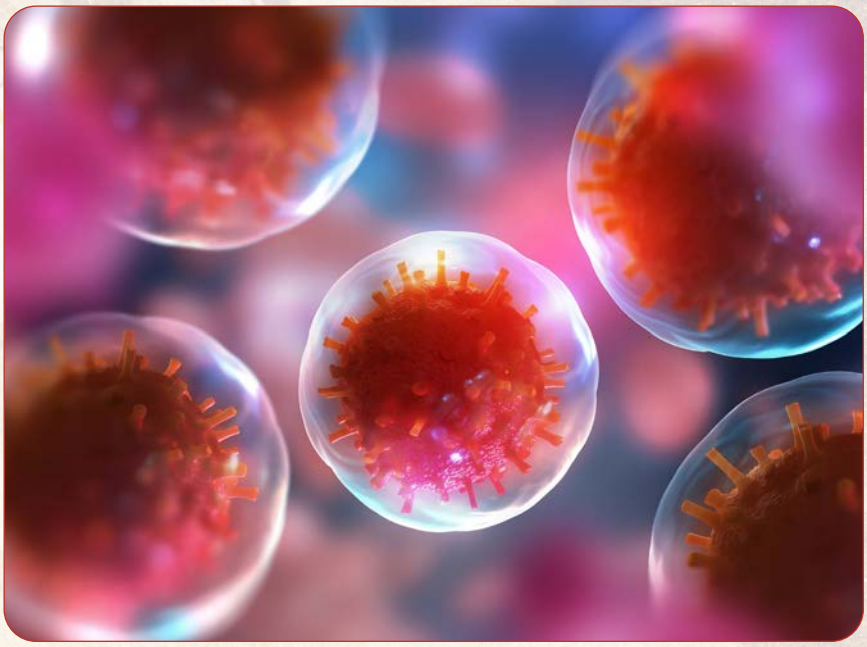
Ciclosporin (Neoral®, Sandimmun®) is a powerful immunosuppressive drug that was first used to help prevent rejection in organ transplant patients. In 1997, the US Food and Drug Administration (FDA) approved the use of ciclosporin for adults with severe psoriasis and otherwise normal immune systems. Ciclosporin suppresses the immune system and slows down the growth of certain immune cells. It is most often used in refractory psoriasis which has failed to respond to other systemic treatments.

Ciclosporin is thus another powerful weapon in the expanding armoury of treatments for psoriasis. As with other powerful medications, there are potentially serious unwanted effects, including high blood pressure, kidney damage and an increased susceptibility to infections.

The 1990s also saw the introduction of another important class of drugs, the Vitamin D analogues, which are for topical (applied to the skin) use and come in ointment, cream, gel and lotion applications. Note that these are not the same as the oral vitamin D supplements that you might take. Topical vitamin D treatments work by slowing down the over-production of skin cells (epidermal hyperplasia) which is the hallmark of psoriasis, and encouraging normal skin growth. They also have an anti-inflammatory effect.

There are four vitamin D treatments available in the UK – calcipotriol (Dovonex®}, calcitriol (Silkis®), tacalcitol (Curatoderm®) and a calcipotriol/steroid combination (Dovobet®).

2000-present – the advent of novel biologics



By far the most exciting development in the management of psoriasis has been the advent of biologics. The first two biologic agents - for the treatment of moderate-to-severe chronic plaque psoriasis - were approved by the FDA in 2003. There are currently around a dozen of these agents – including adalimumab (Humira®), etanercept (Enbrel®), ustekinumab (Stelara®), and secukinumab (Cosentyx®). The UK's National Institute for Health and Care Excellence (NICE) has recommended that these drugs can be prescribed for people with severe psoriasis who have not responded to other systemic treatments such as methotrexate, ciclosporin and PUVA. Biologics must be given by injection (or infusion) - they cannot be taken by mouth.

The latest class of biologics, known as Janus kinase (JAK) inhibitors – e.g. tofacitinib (Xeljanz®) – have a unique mode of action, in that they interrupt signalling between the cytokines responsible for the inflammatory response in psoriasis. JAK inhibitors may be especially beneficial in the management of psoriatic arthritis.

Biological therapies cannot be made simply by mixing various ingredients in a laboratory, the way conventional drugs are made. Instead, biologic therapies are made using living organisms, such as bacteria, yeast, and even mammalian tissue and cells. Insulin is a good example of a biologic treatment used in diabetes.

In addition, the mode of action of biologics is quite different from traditional systemic drugs that impact (and suppress) the entire immune system. Instead, biologics only target specific parts of the immune system. The biologics used to treat psoriatic disease block the action of a specific type of immune cell called a T-cell, or they block inflammatory proteins (cytokines) such as tumour necrosis factor-alpha (TNF-alpha), and interleukins (17A, 12 and 23). These cells and proteins all play an essential role in the development of the skin and joint manifestations of psoriasis.

Not all the latest drugs for psoriasis are classified as biologics. In 2016, apremilast (Otezla™) was approved for use in the UK. It is a systemic (oral) medication that can be used to treat moderate to severe psoriasis and psoriatic arthritis. Its precise mode of action is not entirely clear, but it is known to block an enzyme known as phosphodiesterase 4 (PDE 4), which is involved in the inflammatory response within the cell. Reducing the intensity of the inflammatory response in this way can help to improve symptoms in those with psoriasis and psoriatic arthritis.

Conclusion

Progress in science is always uneven, but our understanding of psoriasis as primarily an inflammatory condition has evolved at astonishing speed over the past few decades. Historically, treatments were often stumbled upon by chance and, in practice, were very blunt instruments which had potentially serious side-effects.

Today, a much more secure scientific foundation has opened the door to a new generation of targeted therapies – aimed at specific molecules in the inflammatory cascade. Consequently, our ability to treat patients and improve their quality of life has never been better. The history of psoriasis is, at the same time, the history of scientific progress.

Dr WD Ashton MD PhD

Health technology assessments

When you take a medicine or treatment to alleviate symptoms you have, or when you are given medication to prevent a future event, you are at the end of process which has often taken many years to achieve.

From discovery, basic research, testing and, eventually, approval to use a treatment, are processes that all have various protocols, rules and legislation to make sure that the product works and is safe.

A process which has to be completed is the health technology assessment (HTA) research. HTA research is undertaken when evidence exists to show that a technology can be effective. The purpose of an HTA study is to establish the clinical and cost-effectiveness for the NHS in comparison with the current best alternative(s). In the UK this is undertaken by the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC), the All-Wales Medicines Strategy Group (AWMSG) and in Northern Ireland, the Department of Health (DoH). Prior to the HTA process, drugs and devices need to be licensed, which falls under the Medicines and Healthcare products Regulatory Agency's (MHRA) responsibilities.

Beyond the UK there are similar health technology assessment and drugs agencies that provide advice to their health providers and reimbursement agencies. Most notably, in the United States the Food and Drug Administration (FDA) is responsible for protecting the public health by ensuring the safety, efficacy and security of human and veterinary drugs, biological products and medical devices, and by ensuring the safety of the country's food supply, cosmetics, and products that emit radiation. For Europe, the European Medicines Agency (EMA) provides evaluations of marketing-authorisation applications submitted through the centralised procedure to provide the basis for the authorisation of medicines in Europe.

To bring many of these agencies and groups together, Health Technology Assessment international (HTAi) is the global, non-profit, scientific and professional society for all those who produce, use or encounter health technology assessments. It represent 82 organisations and more than 2,500 individual members from 65 countries around the world.

HTAi is a member-driven organisation, representing a variety of stakeholders who have interests in HTA. These stakeholders include researchers, policy makers, industry, academia, health service providers, agencies and patients, and they contribute to balanced conversation around HTA across different areas of practice and jurisdictions.

The main event in the HTAi calendar is the annual

meeting. In 2021, the meeting was held in June. Originally set to be hosted in Manchester as a face-to-face meeting, following the global pandemic, the meeting was held as a virtual event.

The main theme of adaptive approaches to HTA was supplemented by three plenary themes:

- Evidence for HTA: Innovative Methods for Challenging Times
- Patients at the Heart of Innovation
- Innovating HTA to support Novel Interventions.

The 2021 annual meeting focused on how HTA can continue to provide the cornerstone in leading health systems innovation, particularly as technologies advance and novel interventions rapidly emerge. As our technological world evolves and new challenges appear, HTA will need to adapt to ensure it continues to be a conduit to support technology innovation.

Innovation in the approach, pace, and scale of health technology development is rapid. As decision-makers respond to the pressures of not only meeting the essential needs of local health systems but also providing progressive and world-class care, traditional approaches to HTA are being challenged.

Collaboration - in developing HTA in emerging regions and developing novel approaches to HTA in systems with established HTA - is essential to the goal of supporting patient access to evidence-based healthcare, particularly as diagnostic and treatment pathways become ever more complex. Through the three aforementioned sub-themes, the meeting explored opportunities presented across global health systems for sustained use of HTA.

It provided an opportunity for researchers, policymakers, healthcare practitioners, technology developers and patients to reflect on how they might innovate at regional and local level across the core HTA elements of evidence, methods, and decision-making.

Background for the meeting

The role of patients was particularly highlighted in the second plenary session. This followed a call for action from a 2019 HTAi workshop for HTA agencies and all stakeholders, including patients, to work together with shared purpose, to change the culture in HTA bodies, with greater patient involvement and alignment with HTA agency goals to improve health outcomes.

In the session Patients at the Heart of Innovation, which had speakers from a variety of specialities, there was agreement that patients need to be part of the assessment process at all stages as they provide vital input to the 'lived experience' of having a condition and how that qualitative insight can provide useful knowledge that perhaps isn't always obvious through quantitative clinical research.

It was also clear that shared understanding across settings with emerging patient engagement practices may highlight opportunities for ensuring meaningful engagement.

The 2022 HTAi annual meeting will be held in Utrecht, Netherlands on June 25-29. The meeting will offer a hybrid event with on-site and virtual access. The main theme will be ***Lifecycle Approach: Coming Together to Make it Happen.***

For more information, visit the HTAi website: https://htai.org

Transforming artificial intelligence

The Medicines and Healthcare products Regulatory Agency (MHRA) is updating regulations applying to software and artificial intelligence (AI) as a medical device.

These measures demonstrate the UK's commitment, following the exit from the European Union, to drive innovation in healthcare and improve patient outcomes.

The exciting and fast-developing field of software and artificial intelligence (AI) as a medical device has an increasingly prominent role within health systems. Applications of AI to be regulated as medical devices can range from screening, to diagnosis, to treatment, and to management of chronic conditions. Regulatory measures will be updated to further protect patient safety and take account of these technological advances.

The MHRA has developed an extensive work programme to inform regulatory changes, including key reforms across the software-as-a-medical-device lifecycle, from qualification to classification, to requirements that apply pre- and post-market. This programme will consider challenges and opportunities posed by AI as a medical device, ensuring these devices are appropriately evidenced and address issues of human interpretability (lack of transparency of AI) and adaptivity (retraining of AI models).

These bold reforms will ensure that patients and public are protected and provide manufacturers with clear guidance to interpret requirements as well as the tools to demonstrate conformity. The changes will transform medical device regulation as it applies to software and AI, providing a regulatory system that is robust and dynamic for the future.

The minister for innovation, Lord Bethell, said: *"While the UK remains a leading destination for cutting-edge healthcare, we are always searching for new and innovative ways we can improve the health and care system for NHS patients. Software and artificial intelligence in medical devices offer the potential to transform people's lives and these updated regulations will make a significant difference in the diagnosis and treatment of a variety of conditions. I look forward to seeing the tangible impact these changes will have on improving patient safety and care for years to come".*

MHRA director of devices Graeme Tunbridge said: *"... an exciting step change in the regulatory approach in this fast-moving area underpins the MHRA's commitment to support responsible innovation that champions patient safety. Reforms will build on wider changes to medical device regulation already underway. We have also today launched our public consultation on proposed legislative changes in the consultation on the future regulation of medical devices in the United Kingdom and we are encouraging everyone with an interest in these products and the way they are regulated to contribute their views. We will continue to evolve our regulations and guidance to respond to this fast-paced field and carry out further research into how best to manage the challenges posed by artificial intelligence as a medical device."*

In addition to the overhaul of the regulations for AI and software as a medical device, the BEIS announced that the MHRA is receiving a grant from the Regulatory Pioneers Fund.

The grant for £194,000 supports the MHRA's drive to become a global leader in regulating this field by carrying out further research into how adaptive AI algorithms in medical devices 'change' and how to regulate their decisions.

The MHRA is helped in bringing forward this programme of change thanks to support from NHSX (joint unit of NHS England and DHSC) and partners such as NICE, and input from academic and industry partners.

Source:
MHRA

PAPAA, working through our Connect Immune Research partnership, is excited to be part of an innovative new grant call, which brings significant new investment into autoimmune research with the ultimate aim of developing new treatments for multiple autoimmune conditions faster.

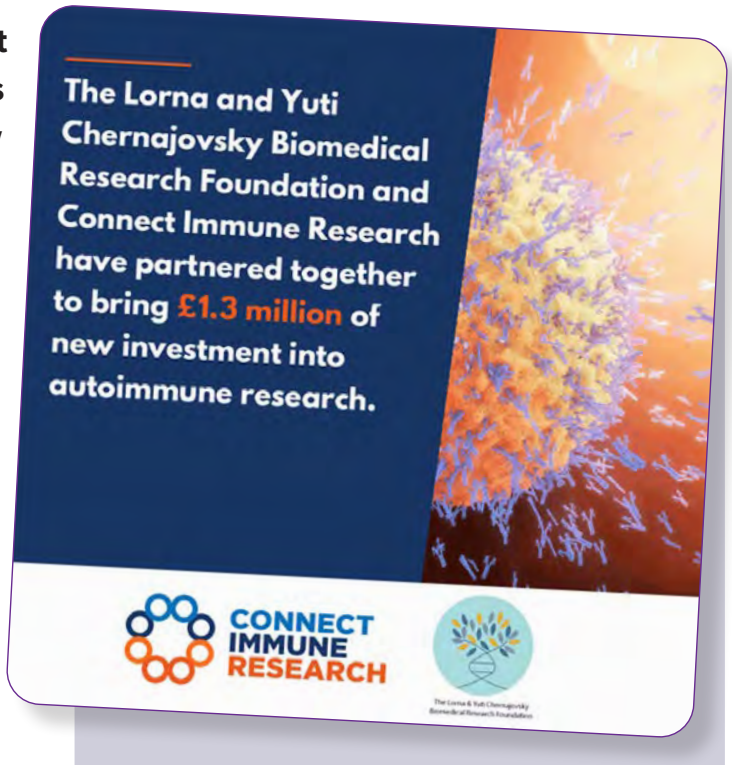
Through our research collaboration, we've partnered with a charitable trust called the Lorna and Yuti Chernajovsky Biomedical Research Foundation to work together to provide £1.3 million of new funding for research into the underlying causes of autoimmunity.

Autoimmune conditions affect an estimated four million people in the UK – equivalent to more than 6% of the population – but are currently incurable.

In all autoimmune conditions, our immune systems attack healthy cells. This new innovative research funding opportunity aims to bring together researchers of these various autoimmune conditions to pool their knowledge and uncover the common threads in their work. Our hope is that this will drive our knowledge forward and help us uncover potential new treatments that could be used for multiple autoimmune conditions.

People affected by autoimmune conditions will be at the heart of this initiative, with representatives already involved in shaping the priorities for this funding call. All partners are committed to ensuring this continues, with the voice of patients being represented throughout all funded research.

We're very proud of this partnership with Connect Immune Research and the Chernajovsky Foundation. By working together, we can beat autoimmune disease faster and bring about real benefits for patients in the shape of new treatments.



About:

The Lorna and Yuti Chernajovsky Biomedical Research Foundation was set up in 2019 to improve public health by providing grants to support high-quality biomedical research into the development of new targeted biomedical therapies.

Connect Immune Research is a partnership of charities dedicated to tackling autoimmune conditions. Members include the type 1 diabetes charity JDRF, Versus Arthritis, MS Society, British Society for Immunology, Alopecia UK, Coeliac UK, Psoriasis and Psoriatic Arthritis Alliance (PAPAA) and Bowel Research UK.

More information:

https://www.papaa.org/news/

Funded by the Innovative Medicines Initiative (IMI), the Fraunhofer Cluster of Excellence Immune-Mediated Diseases (CIMD), together with 25 European partners from research, pharmaceutical companies, SMEs and patient organisations, is researching a poorly understood disease that affects millions of people.

By looking into the disease mechanisms of psoriatic arthritis, the 26 European partners collaborating in the new research project HIPPOCRATES aim at improving diagnostic and therapeutic options for patients living with this condition. Through gaining a better understanding of the complex interplay between clinical and environmental factors, genotype and molecular pathways, the team aims to enable earlier diagnosis and a more accurate prediction of disease progression. This will revolutionise treatment and deliver profound patient benefits.

Overall, it is increasingly recognised that psoriatic arthritis is associated with multiple comorbidities, particularly those affecting mental health, such as depression, and those which promote the development of accelerated atherosclerosis and contribute to the observed increase in cardiovascular morbidity and mortality. Psoriatic arthritis most commonly develops on a background of established skin and/or nail psoriasis, however it can be difficult to diagnose as there are no diagnostic criteria or laboratory tests available. This can contribute to diagnostic delay and poor outcomes. Psoriatic arthritis is characterised by considerable heterogeneity with regards to clinical features, disease progression and response to targeted therapies. Future treatments will need to focus on earlier disease stages and be selected on the basis of detailed patient molecular profiling so as to limit poor long-term outcomes and possibly prevent the development of psoriatic arthritis altogether.

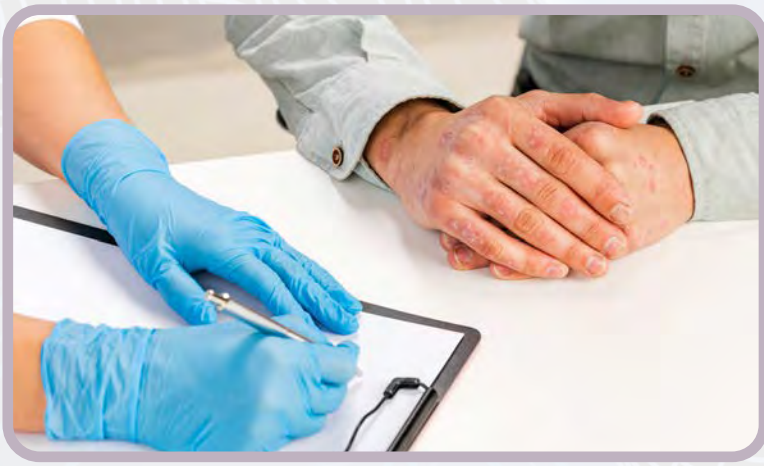
Three Fraunhofer institutes of the Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD (Fraunhofer ITMP, IAIS and IGD) participate in the European HIPPOCRATES (Health Initiatives in Psoriasis and PsOriatic arthritis ConsoRTium European States) consortium, which was launched in order to identify patients at risk of developing psoriatic arthritis, and to develop diagnostic methods and personalised approaches to treat patients.

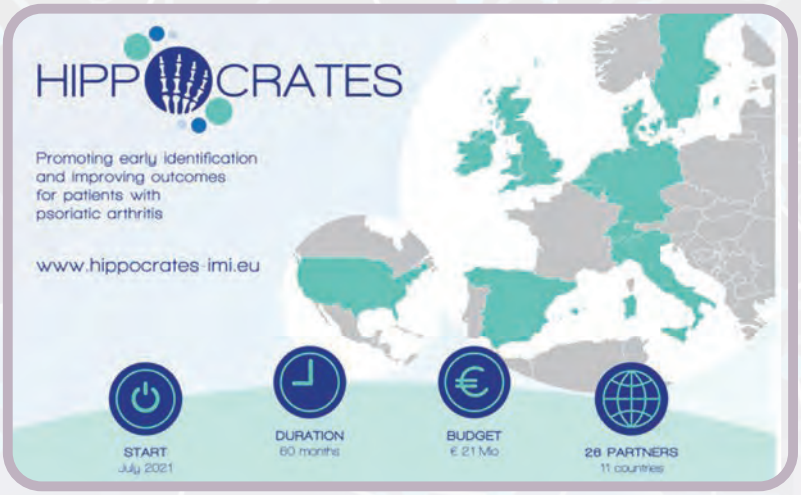
Formed as a transdisciplinary consortium, the project team comprises 26 partner institutions from Belgium, Denmark, Germany, Ireland, Italy, Spain, Sweden, Switzerland, the Netherlands, the United Kingdom and the United States of America. Led by University College Dublin, the partners contribute a diverse range of backgrounds, including clinical, scientific, data analytics, ethics, and patient participation, as well as SME and pharmaceutical industry expertise, in pursuit of the ambitious goals set for the HIPPPOCRATES project.

The project will run for a period of five years with a total budget of €21 million provided by IMI 2 JU, a public-private partnership established as a joint undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Of the total budget, 50% is contributed by the EFPIA partners (Novartis [EFPIA lead], UCB [EFPIA Co-lead], Pfizer and BMS) and 50% by the EU.

"We anticipate that the advances provided by HIPPOCRATES will result in significant new developments that improve patients' quality of life," says Prof Oliver FitzGerald, Newman clinical research professor at University College Dublin, Conway Institute for Biomedical and Biomolecular Research, Ireland coordinator of the HIPPOCRATES consortium.

Co-coordinator, Prof Stephen Pennington, professor of proteomics at University College Dublin and also in the Conway Institute, notes ***"The advances will include the identification of sub-populations and endotypes, the validation of existing and identification of new biomarkers, improved imaging options and the development of a sustainable infrastructure for future PsA research."***





"HIPPOCRATES offers the great promise of powerful new tools to advance both early diagnosis and treatment of patients with psoriatic arthritis. Additionally, and to further its effectiveness, HIPPOCRATES retains the focus on the patient, involving patient research partners within all aspects of the project," adds Denis O'Sullivan of the patient representative arm of GRAPPA-EU.

"This public-private partnership is a great opportunity to decipher this highly heterogeneous disease, and to enable the development of novel PsA therapies and treatment strategies including precision medicine approaches," adds Dr Christine Huppertz, senior principal scientist in the disease areas autoimmunity, transplantation and inflammation at Novartis, and EFPIA lead of the consortium.

In order to achieve its goals, the HIPPOCRATES project will set up a single integrated database combining the cohorts and datasets of the most important European psoriatic arthritis studies and establish a Europe-wide library of relevant clinical biosamples. HIPPOCRATES will also establish a large, prospective, observational study of 25,000 patients with psoriasis who will be recruited and followed online for development of PsA, with patient-centric blood sampling at defined intervals. Furthermore, the team of experts will evaluate and validate newly discovered biomarker signatures for the early diagnosis of PsA, for the identification of psoriasis patients at risk of developing PsA, for the identification of PsA patients at highest risk of damage progression, and for personalised or stratified treatment strategies so as to maximise treatment response. Overall, HIPPOCRATES places particular emphasis on the involvement of patients, clinicians, primary care practitioners, regulators, SMEs (ATTUROS Limited, Oxford Biodynamics Limited and NEOTERYX Limited) and relevant large industry to meet the needs of all stakeholders and to maximise the project's impact.

Fraunhofer ITMP, in cooperation with University Hospital Frankfurt's department of rheumatology, was involved at an early stage in planning the content and institutional composition of the consortium. Together with its Fraunhofer CIMD partner institutes, Fraunhofer IAIS and IGD, it will lead two of the seven HIPPOCRATES work packages, covering 'Early diagnosis of psoriatic arthritis' and 'Data integration and analysis'. For the early diagnosis of PsA, the Fraunhofer team will determine clinical, imaging, and molecular disease features and capture them in a combined context to derive algorithms for psoriatic arthritis diagnosis. Data integration and analysis will involve the use of machine learning to model an AI-based risk score of progression from psoriasis to psoriatic arthritis, as well as a risk score for rapid bone-damaging disease progression and a response score to predict response to a given treatment.

"HIPPOCRATES offers us the opportunity to collaborate with leading European experts to gain a deeper understanding of PsA in order to improve the mobility and quality of life of many affected patients," says PD Dr Frank Behrens, head of clinical research at Fraunhofer ITMP and member of the Fraunhofer CIMD board of directors. ***"I am confident that in our project we will discover new markers that will enable early detection of psoriatic arthritis improve treatment response and possibly even open up avenues for disease prevention. With the unique combination of the diverse expertise represented in Fraunhofer Health Research, from medicine to multi-omics, and image processing to data sciences, we can make an important contribution to manage the debilitating psoriatic arthritis disease."***

Source:
Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP)

Marketplace

Promotional material

If you are thinking about supporting PAPAA or raising awareness on behalf of PAPAA about psoriasis and/or psoriatic arthritis, why not check out some of the merchandise we have available?

www.psoriasis-shop.org

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papaa

PAPAA's position on pharmaceutical funding

PAPAA does not receive funds (either directly or in kind) from the pharmaceutical industry or commercial sector. All activities are funded via donations, subscriptions, charitable grants, legacies or other income generation. We believe that this allows us to act in an open, non-biased way and free from any perceived influence or agendas that may arise. We do not link our activities to commercial marketing or public relations campaigns and will only link our name or logo to an activity if we believe it is beneficial to our constituent group.

Supporting PAPAA

As a charity, in order to continue our work, we need to raise funds. Apart from direct donations, there are other ways to help us too.

AmazonSmile is particularly easy – and free to you. AmazonSmile donates 0.5% of your total purchase to us as a charitable donation. So, it doesn't cost you anything.

You may also be interested in other ways to support us online, such as JustGiving, The Charities Aid Foundation (CAF),

Total Giving, PayPal Giving Fund, Give a car, Easyfundraising, Easysearch and Everyclick. Links to these sites can also be found at:

https://www.papaa.org/donate/ways-to-support-papaa/

Join the conversations

If you have a social media presence, then why not follow us and join the conversation to see what others have to say? The following are the links to our pages:

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Pinterest:	**www.pinterest.co.uk/psoriasisuk**
Instagram:	**www.instagram.com/the_papaa_eye**
LinkedIn:	**www.linkedin.com/company/papaa/**