The Treatment Landscape of Atopic Dermatitis: Interviews with Three Consultant Dermatologists

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Disclosure: Dr McPherson has received support for speaker fees and conference attendance from AbbVie, LEO Pharma, Novartis, and Sanofi. Dr Wali has been an investigator in AbbVie and PellePharm clinical trials; and has taught at sessions sponsored by LEO Pharma and UCB. Dr Laws has received honoraria and/or grants as an investigator, speaker, and/or advisory board member for AbbVie, Actelion, Almirall, Celgene, Janssen, LEO Pharma, Lilly, Novartis, Sanofi, and UCB.

Acknowledgements: Medical writing assistance was provided by Dr Brigitte Scott, MarYas Editorial Services, Cowlinge, UK.

Disclaimer: The opinions expressed in this article belong solely to the named interviewees.

Support: This article is sponsored by Sanofi Genzyme, with no input on editorial content except for a check on factual accuracy.

Citation: EMJ. 2021;6[1]:23-32.

Interview Summary

Atopic dermatitis (AD), sometimes referred to as 'atopic eczema', is a common, chronic, pruritic, Type II inflammatory skin disease which is associated with immune dysregulation and skin barrier dysfunction.[1-4] Individuals with moderate-to-severe AD have an overactive immune system, which results in signs and symptoms such as an intense, persistent itch associated with dryness, cracking, redness, crusting, and oozing of the skin.[5] AD may occur at any age but is more commonly seen during childhood, with a frequency of 10–30%.[6] Among adolescents, the estimated prevalence of AD is 8.7–18.1% in the USA,[7] 10.0–15.0% in the UK,[8] and <10.0% in most European countries.[8] The prevalence of AD in adults is 1.0–3.0%.[9] Risk factors for AD include female sex, sensitisation to inhalant and food allergens, allergic asthma and/or rhinoconjunctivitis, and the practice of certain jobs.[6] In the majority of patients, AD is lifelong (although there can be long periods of remission, recurrence is common) but not permanently debilitating and the disease can modify through life, which makes treatment of AD particularly challenging.

For this article, EMJ conducted interviews in July and August 2020 and January 2021 with three consultant dermatologists, Dr Tess McPherson, Dr Gorav Wali, and Dr Philip Laws, all of who have a wealth of experience and expertise in managing AD, to gain their perspectives on a range of topics in this area. The experts gave valuable insights into several pertinent issues in AD treatment and discussed significant recent developments in the field.

The article discusses the current treatment landscape for AD and evaluates where new biologics fit into this landscape. Strategies to maximise the use of currently available therapies are explored and the impact of the coronavirus disease (COVID-19) pandemic on dermatology services and treatment of AD is assessed.

ATOPIC DERMATITIS: IMPACT AND IMPORTANCE OF TYPE II IMMUNITY

Impact of Atopic Dermatitis

AD is associated with significant comorbidity and economic burden,[10] and significantly affects quality of life.[6,11] Although the huge quality of life impact is evident to the patient and their family, the extent of the impact may not always be perceived by healthcare professionals. The associated itching, sleepless nights, affected concentration, decreased school attendance, social isolation, and bullying have a massive impact on the overall health, quality of life, and educational attainment of children with AD. Additional, significant issues for adults with AD are absenteeism (through appointment attendance and inability to go to work because of infected skin) and presenteeism (disrupted productivity at work because they are distracted by their skin condition and cannot function at their normal level). Furthermore, Dr Laws noted that patients with AD are often conscious of the cosmetic impact of their condition, particularly if their skin is affected at high-impact sites, such as the hands, face, and scalp, which may be associated with significant shedding of scale. This widespread skin condition has been associated with mental health disorders, including anxiety[6] and attention deficit (hyperactivity) disorder[12,13] in adults and children. According to Dr Wali, atopic disease affects the whole family concerning distressed patients, time and cost of treatments, and inconveniences such as greasy bedsheets so it is important to engage, educate, and support patients and their families. Dr Laws estimated that up to one-quarter of general practitioner (GP) consultations are skin-related,[14] with patients with AD making up a significant proportion of cases,[14] and reattendance for the same problem is common[15] thereby underscoring the massive economic and healthcare burden of this condition.

Type II Immunity in Atopic Dermatitis

Dr McPherson explained that barrier dysfunction, irritant avoidance, and the concept of Type II immunity are important aspects of AD which need to be addressed and that reducing inflammation in AD is key. Dr Wali added: "Type II immunity is central to AD, but it is very complicated in terms of how it interacts with barrier function, the microbiome, and the environment and we are only just starting to piece it all together."

CURRENT TREATMENT LANDSCAPE

Topical and Systemic Treatments

Dr McPherson explained that most of her patients are referred through their GP or paediatrician and are often undertreated with basic therapies, such as intermittent use of anti-inflammatory topical agents, particularly steroids, and overuse of antibiotics. According to Dr McPherson, mild AD can often be managed very successfully with emollients, topical steroids, and patient education. In patients whose AD is not controlled with this approach, systemic treatments are routinely used, with methotrexate (MTX) a common first-line therapy.[16] If MTX is ineffective, or when side effects or the associated repeat blood testing are not tolerated, patients may receive biologics. Dr McPherson explained: "I see around 40 patients with moderate-to-severe AD per week and no more than an estimated 5–10% of patients require systemic treatments or biologics. The majority can be managed with topical treatments and patient education and if these were initiated earlier, we may be able to modify disease more systematically."

Dr Wali considered: "It is an exciting time for management of AD because there is such a broad range of treatments available and lots of new therapies on the horizon." He described the current treatment landscape as ranging from quite basic topical therapies, such as emollients, soap substitutes, cleansing baths, and topical steroids, to phototherapy, oral immunosuppressants, and ultimately, biologics and targeted therapies, such as JAK inhibitors. Dr Wali follows an integrated care pathway for AD that is dictated by the National Institute for Health and Clinical Excellence (NICE) guidelines.[17] The guidelines divide the care pathway into patients aged ≤12 years and those aged >12 years and provides guidance on how to manage AD particularly in primary care, clinical diagnosis, when to consider further investigations, and when to refer to secondary care.[17]

In agreement with Dr McPherson, Dr Wali said: "Although the treatment landscape is very broad, the vast majority of patients,

particularly paediatric patients, are managed on the first step of the ladder, with emollients, soap substitutes, topical steroids, and prompt treatment of infections." Dr Wali outlined that only a tiny percentage of paediatric patients go on to systemic treatments (mostly MTX). A larger proportion of adults seen in secondary care go on to systemic treatments, although this is difficult to define numerically as most patients are GP-referred, having failed to respond to topical therapies. Only a relatively small number of adult patients receive biologics.

Dr Laws indicated there is a "phobia" around the use of topical steroids, with patients reluctant to use these treatments as they thin the skin. He explained that GP and dermatologists educate their patients about skin care and how to treat their skin optimally using topical steroids; however, at dispensing, the last stage, pharmacists may warn patients about the skin-thinning effect of topical steroids. Although appropriate, if overly cautious, this warning may create anxiety, uncertainty, and confusion for patients. Dr Laws highlighted educational gaps in understanding of skin care and treatment. He specified that GP training in dermatology is often limited to a brief introduction to the therapeutic area during undergraduate training and then is mostly supported through learning from other GP and continuing medical education when they are in practice (most GP do not have attachments in dermatology). Similarly, there is also limited substantive formal dermatology training for community pharmacists on how to use topical steroids. This has the potential to result in conflicting messages to patients from different healthcare professionals about their skin care treatment. Unless the story remains consistent, or broadly similar, it unpicks the confidence the patient has in their skin care regimen, so they are left feeling that they are potentially doing things that are risky or dangerous.

New Era of Treatments in Atopic Dermatitis

Biologics are injectable drugs which use an antibody to treat a disease at the immune system level. The biologic dupilumab[18] blocks interleukins from binding to their cell receptors, which keeps the immune system from overreacting, thereby lowering inflammation and decreasing symptoms of AD. Dupilumab was the first, and is currently the only, approved biologic in the European Union (EU) and USA for the treatment of moderate-to-severe AD in adolescents (>12 years) and adults who are candidates for systemic therapy (EU) or who are inadequately responsive to standard of care (USA). The favourable efficacy, safety, and economic impact of dupilumab compared with standard of care for uncontrolled moderate-to-severe AD has been reported.[19] Tralokinumab[20] has shown positive results in Phase III clinical trials, and nemolizumab[21,22] and lebrikizumab[23] are new biologics for AD that showed promising results in Phase IIb clinical trials.

Where do Biologics Fit into the Treatment Landscape for Atopic Dermatitis?

Dr Wali proposed there will always be a need to use topical treatments before receiving biologics as they are easily accessible and a majority of patients with AD can be managed effectively with emollients and topical steroids. Dr Laws noted that several nonsteroidal topical therapies in development also show promise and will potentially move clinicians and patients away from topical steroids. However, whether biologics should come before oral immunosuppressants will be down to safety profile, experience, and cost. Patients receiving oral immunosuppressants need to be monitored and may require many blood tests and may experience potentially severe side effects. There are no major safety concerns with biologics, including dupilumab, apart from conjunctivitis. Dr Wali speculated: "As we gain more experience, maybe biologics could become first-line for moderate-to-severe AD but I foresee oral immunosuppressants will continue to be used before moving on to biologics, particularly because of the cost of treatment."

Continuing this theme, Dr Laws perceived biologics to have a very important role in AD, particularly considering the limitations of systemic therapies, including low response rates, tolerability, and side effects, and the fact that biologics are licensed for AD whereas MTX is not. He stated: "If cost was not a factor, we would be using more novel therapies. The potential for these therapies to transform the lives of patients with moderate-to-severe AD unresponsive to topical therapies is enormous." He explained that some of his patients with severe AD who he has managed for many years and had a 15–

20% improvement on systemic therapy (disease was tolerable) were switched to a biologic and saw enormous improvement in their disease. As an example, Dr Laws referred to one of his first patients with long-term AD who was switched from systemic therapy to biologics. One morning soon after the switch, the patient woke up in a panic because something was missing: after around 20 years of itching, the absence of this sensation was unrecognisable and transformational.

Are Biologics Potentially Disease-Modifying and Can They Prevent Atopic March?

There have been clinically meaningful and statistically significant improvements in AD signs and symptoms, including pruritus, and quality of life with biologics in adolescents with moderate-to-severe AD,[24,25] for whom there are limited treatment options.[26-28] Dr McPherson thought that biologics could be potentially disease-modifying with earlier treatment in younger patients and may prevent atopic march, food allergies, allergic rhinitis, and asthma, but she questioned whether more aggressive early treatment with topical steroids to modify local inflammation could achieve the same result and studies were needed to evaluate this. The BEEP trial showed that emollients administered twice per day to babies aged up to 6 months from high-risk atopic families did not prevent development of AD.[29,30] Dr McPherson added: "Having dupilumab and the future options of other biologics has been a game changer; however, biologics have not been used for long enough to establish whether they are disease-modifying or just stabilise disease, particularly in AD, which typically fluctuates in severity over time." Dr Wali reiterated that Type II immunity is complex, and we do not know whether targeting cytokines will transform AD. Dr Laws suggested that increased understanding of the pathogenesis of AD will enable targeting of specific aspects of the disease pathway, in contrast to historically cruder methods of immunosuppression with drugs such as cyclosporin, MTX, and mycophenolate. Whether this has a disease-modifying effect is an important research question that will need investigation. He stated: "As more treatment options become available for AD, there will be increased understanding of the impact of blocking different parts of the pathway and how this affects not only response but also side effects."

Maximising the Use of Currently Available Treatments in Mild Atopic Dermatitis

Dr McPherson considered: "Development of biologics has made us look at other therapies for AD in more detail and has shown us that topical treatments, if done well and supported by good patient education, can be very effective in mild AD. This is a really important thing to remember."

Dr Wali agreed: "Using basic treatments like topical steroids and emollients that have been around for a long time and are proven to work is important and we need to always remember that they are there. In terms of disease modification, it may be that just using these treatments early and well could help prevent atopic diseases." One of the difficulties with adolescents is they do not want to be different from their peers; they may not want to apply creams and topical treatments. Educating and engaging adolescents with AD and encouraging them to take ownership and control of their treatment can be just as good a way to manage their disease as progressing them on to other therapies.

A Comprehensive Care Package is Needed for Atopic Dermatitis

Dr Laws drew a parallel between AD and psoriasis, a principal element of inflammatory dermatoses, with one of the main differences being psoriasis is an immune-mediated disease whereas AD is immune-mediated with a barrier dysfunction, and the latter is crucial in the development of AD. He referred to AD as the "poor relation to psoriasis" as there are fewer treatment options and limited services for AD compared with psoriasis, for which there have been numerous treatments for the past 15–20 years, and a greater number of dedicated clinics enabling better patient management. There have been some excellent studies investigating AD disease characteristics but the advent of novel therapeutic options for AD, renewed interest, and better investment in this disease area will see greater insights over the coming years. Dr Laws intimated that the relatively slower progress in AD research compared with psoriasis was a result

of AD being perceived as a nuisance skin problem that people grow out of and is consequently not taken seriously enough to warrant appropriate funding and research.

Dr Laws shared his concern about how much suboptimal management of AD in primary care may be impacting on referrals to secondary care. If patients were treated early and optimally in primary care, he reasoned, this may reduce chronic disease burden and circumvent the need for patient referral to secondary care. Once the itch/scratch cycle is established in a patient, it becomes part of a chronic disease pathway and is extremely difficult to reverse. His approach is to treat aggressively in the early phase to control disease, with appropriate support to reduce the risk of skin atrophy and side effects of topical steroids. In a proactive treatment response, patients gain confidence in how to manage their skin disease and avoid suboptimal response, patient fatigue, and disease chronicity associated with a more cautious approach.

According to Dr Laws: "One of the main aspects of AD treatment that is often neglected is ongoing skin care with appropriate use of emollients regardless of coadministered systemic or biologic treatment options." More specialist clinics and support and educational reinforcement from specialist nurses, physician associates, and other healthcare professionals around the importance of continuous and effective skin care is vital to provide optimal care for patients. He added: "There is a need for a comprehensive care package that covers the basic treatments as well as the high-cost drugs, with closer integration and engagement with GP."

GUIDELINES

There are various guidelines for the management of AD.[31-33]

NICE Guidance for Biologics in Atopic Dermatitis

NICE guidance[17] is straightforward for use of biologics in AD: the criterion for biologics is failure to respond to, or contraindication to, a systemic immunosuppressant. Anyone who has had a systemic immunosuppressant for AD is, by definition, someone with moderate-to-severe disease. However, there is a requirement to numerically define improvement on treatment to enable therapy to continue. NICE set a threshold of ≥50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started and ≥4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started.[17]

The NICE guidance is nonspecific in some areas and is therefore open to broad interpretation and can be used flexibly, which may mean that a wide range of treatment pathways/regimens are adopted in the different clinics across the country. Such differences in interpretation of the guidance are not ideal from a patient access perspective. Dr Laws postulated that there is perhaps a need for an open and detailed discussion nationally around the interpretation of the guidelines and the impact on patients and the healthcare system.

Have the Guidelines Kept Up with Progress in Atopic Dermatitis?

The NICE guidelines in AD have not been updated for over a decade. There is a paucity of comprehensive, standardised, and integrated national and local treatment guidelines for AD in the UK. Available guidelines describe siloed primary care AD management and there is a lack of clarity for treatment in secondary care. Recent advances in AD treatment have failed to prompt guideline updates.

There has been great scientific and clinical progress in AD, including the development of biologics, and the field is rapidly changing. Dr McPherson thought the treatment guidelines were keeping up with the introduction of new biologics as far as possible. She explained that good evidence is required for new medicines to be introduced and this may have been stalled by the coronavirus disease (COVID-19) pandemic.

Dr Wali acknowledged that it is early days for biologics in AD and, so far, the guidelines have kept up to date. He admitted it will be trickier when more biologics come through in terms of which ones to use, when, and in whom. He expected the field to change significantly with the introduction of new biologics and the guidelines may struggle to keep up.

DERMATOLOGY SERVICES AND TREATMENT OF ATOPIC DERMATITIS IN THE COVID-19 PANDEMIC

Guidance During the COVID-19 Pandemic

There has been considerable COVID-19-related guidance for patients, including information on teledermatology consultations,[34] and general recommendations[35] from the European Academy of Dermatology and Venereology (EADV) and the COVID-19 resource centre of the European Academy of Allergy and Clinical Immunology (EAACI).[36] When asked whether the guidance has been useful and specific enough during the COVID-19 pandemic, Dr McPherson reflected that the guidelines have been pragmatic and possibly a little overcautious regarding shielding advice but the priority was for patients to be kept as safe as possible based on the available information. Dr McPherson considered: "The guidelines in dermatology have been appropriate and the science has been magnificent. The world of science working together has been great despite not always being supported by politics."

Dr Wali found the British Association of Dermatologists (BAD) Guidelines helpful during the pandemic, particularly the table in which patients are triaged based on immunosuppressants and comorbidities, and the guidance on shielding.[32] He considered that there was a real sense of learning as you go along, and advice regarding shielding, face masks, and swabbing was confusing, so better structures need to be in place to deal with future pandemics.

Changes to Services

The impact of the COVID-19 pandemic on dermatology services has been significant, requiring all participants, including patients, to change. Continuity of patient care, support, and management of disease have been possible using digital technology during the pandemic, and although the service has had to adapt quickly, it has been maintained to a safe degree. Dr Wali explained that apart from improved remote working, the COVID-19 pandemic has prompted the development of a triage system for patient referrals. All referrals require the GP to send photographs of their visible symptoms of the disease and the patient is triaged to keep mild-to-moderate cases in the community and refer more severe cases for further care. For referred patients, the GP also organises community screening blood tests. The triage system enables more care in the community, the patient is more prepared, and more information is available beforehand, thereby minimising appointment times and enabling treatment to start earlier.

Dr Wali acknowledged: "The COVID-19 pandemic had a massive impact on services, but also provided an opportunity to change and improve technology, remote consultations, and email advice." Video consultations and patient-provided photographs are not ideal but assist with diagnosis and are effective for follow-up. Some patients may opt to continue remote consultations, particularly paediatric cases for which home appointments can be easier and more comfortable for the patient and their family.

Video and telephone reviews were also advocated by Dr Laws, who acknowledged the digital technological advances adopted during the pandemic and declared he would like to see "a drive towards more patient-initiated follow-up [with certain parameters in place] for patients whose AD is well controlled to reduce appointment and travel time and lessen appointment fatigue for the patient as well as decreasing the burden on healthcare services."

Dr McPherson surmised: "Routine patient-reported outcomes are not so easily recorded virtually as they are in the clinic, which means there is a lot of information we are no longer capturing. Although the pandemic set up is not ideal, a quick fix, or sustainable, it has been an excellent response to a difficult situation."

Immunosuppressants and Biologics in the COVID-19 Era

All three consultant dermatologists interviewed considered there was not enough evidence to stop the use of biologics during the COVID-19 pandemic; there are no signals that patients on biologics are more likely to contract COVID-19 or experience severe COVID-19. Two small studies conducted in Italy indicated that there is no evidence of increased risk with dupilumab in patients with AD who also have COVID-19.[37,38] Furthermore, the European Task Force on Atopic Dermatitis (ETFAD) did not consider dupilumab

to increase risk for viral infections.[39] There was also no evidence of risk with immunosuppressants in the COVID-19 era, according to studies from Spain[40] and Italy.[41]

Although some patients developed anxiety about using immunosuppressants (usually MTX) and biologics (dupilumab) during the pandemic and decided themselves to stop treatment, the consultant dermatologists did not consider alterations to treatment necessary. Stopping treatment would result in a flare-up, increased exposure to healthcare, and potentially COVID-19.

The pandemic did impact on patients starting immunosuppressants or biologics. These treatments were delayed rather than introduced when there was less access to healthcare for regular blood tests (MTX) and injections (dupilumab).

Dr Laws elaborated on the difference in patient attitude in the first and second waves of the pandemic to explain the probable slight increase in biologics prescribing in the second wave compared with the first. A perceived reluctance to initiate biologics in the first wave paralleled an optimism that the pandemic would soon be over, and patients appeared to delay starting such treatments accordingly. There appeared to be a more balanced view of the pandemic during the second wave and patients received more reassurance from clinicians, who now had a better idea of the nature and impact of the pandemic and a clearer view of the implications of using biologics in this situation. The clearer perspective meant patients appeared to be more willing to consider new treatments. Dr Laws specified that some clinicians appear to have proactively chosen biologics (dupilumab) over standard immunosuppressive therapies because of the perceived risk in the COVID-19 era and that the targeted nature of biologics suggested potentially lower risk, less monitoring, and decreased healthcare contact, all of which are important in a pandemic.

FUTURE PROSPECTS AND CONCLUSIONS

Dr McPherson summarised: "This is an exciting and rapidly moving field. The introduction of biologics for AD has been a major step forward for a minority of patients with recalcitrant, problematic disease that could not be controlled with the available treatments." Dr McPherson's concern was not to push biologics to patients who do not necessarily need them, and she would like to see better alignment and a more scientific approach when new products are introduced. Dr McPherson emphasised: "We should not lose sight that topical steroids can be extremely effective in mild AD and may have a modifying role, and we must ensure research is done in this area before rolling out a more systemic cytokine approach."

Dr Wali highlighted: "The future in AD is exciting, with lots of new treatments coming through targeting the different disease pathways. Increasing understanding of Type II immunity will evolve further treatment options, including for patients who are currently struggling." Dr Wali considered if therapies modify Type II immunity and atopic disease and prevent atopic march, this could potentially transform the management of atopic diseases generally. He added: "Service delivery will change according to technology with remote consultations and follow-up, which will benefit the patients in terms of less travel and will enable delivery of a better service."

Dr Laws considered: "The future for the treatment and management of AD is very exciting. There are around 30 treatments in development, and several current clinical trials are so far showing very positive responses. Biologics are dramatically effective, transformational treatments for patients with moderate-to-severe AD." He described how patients in their working prime who are often unable to work because of their condition are delighted with their response to biologic therapy and the positive impact on their lives. He highlighted: "Some of my patients with AD are suicidal; to be able to tell them about new treatments currently available or in the pipeline that will impact on their condition is incredible. As a clinical community, the challenge we must seek is to balance these therapeutic advances with good skin care education and guidance in conjunction with a comprehensive clinical service meeting the needs of the individual patient."

Biographies

Dr Tess McPherson

Consultant Dermatologist and Senior Clinical Lecturer, Oxford University Hospitals, Oxford, UK

Dr Tess McPherson is a consultant dermatologist, senior clinical lecturer, and clinical lead for Paediatric and Adolescent Dermatology at Oxford University Hospitals (since 2012).

Dr McPherson's medical training included undergraduate medicine at the University of Cambridge, Cambridge, UK, international research working for the World Health Organization (WHO) in South America, and an academic training post at the Weatherall Institute of Molecular Medicine (WIMM), Oxford, UK, studying immunology of eczema. This was followed by a paediatric dermatology training fellowship at Birmingham Children's Hospital, Birmingham, UK.

Dr McPherson was lead clinician on a National Institute for Health Research (NIHR)-funded project to develop a web resource for young adults with skin disease.[42]

In Oxford she has established an award-winning dermatology service with psychological support for adolescents with skin conditions.[43]

Dr McPherson is Secretary (President-Elect) of the British Society of Paediatric Dermatology (BSPD). She is active in national and international paediatric dermatology, including developing clinical guidelines and patient information for the British Association of Dermatology (BAD), monitoring effects of medications on children and young people (BADBIR registry), and works with charities and patient groups.

Dr Gorav Wali

Consultant Dermatologist and Honorary Senior Clinical Lecturer, Oxford University Hospitals, Oxford, UK

Dr Gorav Wali is a consultant dermatologist and honorary senior clinical lecturer at Oxford University Hospitals.

Dr Wali completed undergraduate medical training at Oxford University. He then undertook general medical and dermatology specialist training in Oxford University Hospitals and the Thames Valley Deanery, London, UK. Following appointment as Consultant in Oxford University Hospitals, he has co-led the inflammatory dermatosis service, including the use of biologics, and has developed the paediatric dermatology service. He is actively involved in clinical research and has been principal investigator for clinical trials in eczema and hidradenitis suppurativa.

Dr Philip Laws

Consultant Dermatologist and Senior Honorary Lecturer, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Dr Philip Laws is a consultant dermatologist and senior honorary lecturer at Leeds Teaching Hospitals NHS Trust.

Dr Laws undertook dermatology training in Salford Royal Hospital, Manchester, UK, which included a medical education fellowship. He subsequently completed a medical dermatology fellowship in Toronto, Canada. Following this he was appointed to a consultant post in Leeds where he has co-led the inflammatory dermatosis service. His research interests include psoriasis, atopic dermatitis, and connective tissue diseases. He has been principal investigator and chief investigator in several clinical trials.

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