





# The Role of a Novel Generation of Emollients, ‘Emollients Plus’, in Atopic Dermatitis

Elena Araviiskaia <sup>1</sup>, Carlo Pincelli <sup>2</sup>, Adele Sparavigna <sup>3</sup>, Thomas Luger <sup>4</sup>

<sup>1</sup>Department of Dermatology and Venereal Diseases, First Pavlov State Medical University of St Petersburg, St Petersburg, Russia; <sup>2</sup>DermoLab, Department of Surgical, Medical, Dental and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy; <sup>3</sup>Derma Clinical Research and Bioengineering Institute, Milan, Italy; <sup>4</sup>Department of Dermatology, University of Münster, Münster, Germany

Correspondence: Thomas Luger, Dermatology Clinic, University of Münster, Von-Esmarch-Straße 58, Münster, 48149, Germany, Email [luger@uni-muenster.de](mailto:luger@uni-muenster.de)

**Abstract:** Emollients are the mainstay maintenance treatment for atopic dermatitis (AD). A novel generation of emollients, ‘emollients plus’, containing active, non-medicated substances, has softened the distinction between emollients and topical drugs. A literature search for selected key words was performed using PubMed. Additional papers were identified based on author expertise. Whilst the inclusion of five components of an ideal emollient has been proposed, no such consensus exists for emollients plus and they can vary markedly in their composition and modes of action for AD treatment. This could have a profound effect on their clinical efficacy. The efficacy of emollients plus in restoring and maintaining skin barrier function has been demonstrated on multiple levels, with evidence reported for their effects on the physical and biochemical, microbial, immunological, and neurosensory barriers. When selecting an appropriate AD treatment approach, the safety profiles of the available topical therapies must be carefully considered. There are several proposed treatment approaches for AD, including preventive, proactive, intermittent, and synergistic approaches. Emollients plus may be effective not only as maintenance therapy for AD, but also when used synergistically with anti-inflammatory pharmacological therapies.

**Keywords:** atopic dermatitis, atopic march, emollient, emollient plus, maintenance therapy, skin barrier

## Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by dry skin, intense itching, and inflammatory skin lesions, and can be highly heterogeneous in presentation.<sup>1–3</sup> AD can present with frequent spontaneous flares and remissions.<sup>1,4,5</sup> It is one of the most common non-communicable skin diseases, affecting up to 20% of children and 2–8% of adults.<sup>6</sup>

The skin is made up of multiple layers, and forms a physical, biochemical, microbial, immunological, and neurosensory barrier between the internal and external environments.<sup>7</sup> The epidermis, comprising the stratum corneum, stratum granulosum, stratum spinosum, and the stratum basale, is the main component of the skin’s protective barrier.<sup>7</sup> In AD, epidermal morphology and stratum corneum lipid composition are altered, and skin barrier function is impaired, with increased transepidermal water loss (TEWL) and increased percutaneous penetration. AD is also associated with T helper (Th)2-predominant inflammation.<sup>8–10</sup>

Emollients are the mainstay for AD management: maintenance of stable disease can be achieved with emollients after induction of remission with anti-inflammatory treatment.<sup>6</sup> Emollients are topical formulations with vehicle-type substances lacking active ingredients,<sup>6</sup> and act by providing a barrier for skin affected by AD, retaining moisture and protecting it from irritants.<sup>11</sup> Emollients usually contain petrolatum, paraffin, glycerine, and plant-derived butter and oils.<sup>11</sup> They can be classified as first, second, or third generation based on their composition and mode of action. First-generation emollients, such as petrolatum, paraffin oil, and fatty alcohols, are hygroscopic and occlusive; second-generation emollients, such as glycerol, sorbitol, and natural moisturizing factor substitutes, restore hydration and barrier function; third-generation emollients, such as physiological lipids, repair the skin barrier.<sup>12</sup>

The development of a novel generation of emollients containing active non-pharmacological ingredients, ‘emollients plus’, has softened the distinction between emollients and topical drugs.<sup>6</sup> Dermoflan AD emollient plus cream (Meda Pharma, Solna, Sweden; herein referred to as EC) is an example of an emollient plus specifically formulated for skin affected by AD. It contains several active ingredients to target multiple mechanisms in AD pathophysiology: licorice extract (glycyrrhizinic acid) has anti-inflammatory properties;<sup>13</sup> niacinamide, sterols, glycosphingolipid, and *Linum* seed oil act to restore barrier function;<sup>14–16</sup> xylitol and galacto-oligosaccharide have selective antibacterial and prebiotic activity to maintain the skin microbiome;<sup>17–19</sup> and laureth-9-polydocanol reduces itching.<sup>20</sup>

Given their integral role in AD management and the increase in commercially available products, this review aims to provide an overview of the composition and efficacy of emollients plus, with a particular focus on EC. We also provide an overview of the necessary safety considerations when selecting a treatment approach in AD.

## Methods

A virtual focus meeting, attended by the authors, on dermocosmetics in AD was held in October 2021. The discussions resulting from that meeting formed the basis of this review. After agreeing the scope of this review, computerized searches were undertaken in PubMed, using the search term atopic dermatitis in combination with: Dermoflan AD, emollient, emollient plus, moisturizer, skin barrier, atopic march, flare, time to flare. Additional papers were identified based on author expertise. Only papers deemed directly relevant were included in this review.

## Results

### Emollients Plus

An emollient plus is a topical formulation with vehicle-type substances and active, non-medicated substances, such as saponins, flavonoids, and riboflavins from protein-free oat plantlet extracts, and bacterial lysates.<sup>6</sup> Emollients plus can improve AD lesions through several synergistic modes of action, including preserving barrier lipid content,<sup>21</sup> preventing TEWL, and moisturizing the skin,<sup>14,21</sup> reducing inflammation,<sup>20,22</sup> and reducing itch.<sup>20</sup>

Thirteen emollients plus of interest were identified. Below, their compositions and clinical efficacy have been compared.

### The Composition of Emollients Plus

It has previously been suggested that the ideal emollient contains five key components: humectants, non-physiological lipids (eg, mineral or vegetable oil), physiological lipids (eg, ceramides, free fatty acids), anti-pruritics/soothing agents, and agents that support epidermal differentiation.<sup>23</sup> This has recently been reviewed: the authors concluded that the concept of five components in an emollient for dry skin remains valid<sup>24</sup> and highlighted the benefits of dexpanthenol to compensate for reduced hydration and enhance epidermal differentiation. They also recommended further exploration of substances targeting enzymes responsible for the synthesis or elongation of lipids. The need to develop different formulations for use in various environments (eg, by season/climate and skin site affected) was also emphasised.

Whilst the inclusion of five components has been proposed for emollients, no such consensus exists for emollients plus, which vary markedly in their composition and modes of action (Table 1).<sup>11,13,14,16–20,24–53</sup> Given this heterogeneity, variability in the effects of emollients plus on AD is unsurprising.

### Clinical Efficacy of Emollients Plus

Ten studies on nine emollients plus were identified, reporting data on average time to flare and/or flare-free period (Table 2).<sup>26,28,38,41,42,46,49,54–56</sup>

The longest average time to flare was reported with Eucerin Eczema Relief Body Crème plus cleanser (Eucerin, Hamburg, Germany) and Canoderm cream 5% (ACO HUD Nordic AB, Upplands Väsby, Sweden), with an average time to flare of >180 days for both (mean was reported for Eucerin Eczema Relief Body Crème; median was reported for Canoderm cream 5%).<sup>41,42,56</sup> However, in a separate study, the median time to flare for Canoderm cream 5% was just 22 days.<sup>41</sup>

**Table 1** Active Substances and Proposed Mode of Action of Commercially Available Emollients Plus

| Emollient Plus (Company)                       | Active Substances  | Proposed Mode of Action for AD Treatment  |
|--|--|---|
| A-DERMA Exomega Control (Pierre Fabre)         | Rhealba oat plantlet extract, L-ALA-L-GLU dipeptide, hyaluronic acid <sup>25</sup>                                       | <ul style="list-style-type: none"> <li>• <b>Rhealba oat plantlet extract with L-ALA-L-GLU dipeptide</b> is anti-inflammatory and has healing properties for fragile skins with an imbalanced or damaged barrier<sup>25</sup></li> <li>• <b>Hyaluronic acid</b> supports tissue development and wound healing<sup>25</sup></li> </ul>  |
| Atoderm Intensive cream (Laboratoire Bioderma) | Vitamin B3, palmitoyl ethanolamide, $\beta$ -sitosterol, zinc, ceramides <sup>26</sup>                                   | <ul style="list-style-type: none"> <li>• <b>Vitamin B3</b> increases skin lipid production<sup>26</sup></li> <li>• <b>Palmitoyl ethanolamide</b> is an anti-pruritic agent<sup>26</sup></li> <li>• <b><math>\beta</math>-sitosterol</b> is an anti-inflammatory agent<sup>26</sup></li> <li>• <b>Zinc</b> is known for its antibacterial action against <i>Staphylococcus aureus</i><sup>26</sup></li> <li>• <b>Ceramides</b> enhance lipid integration into the skin barrier<sup>26</sup></li> </ul>   |
| Atopiclair (Sinclair Pharma)                   | Hyaluronic acid, shea butter, glycyrrhetic acid, extract of <i>Vitis vinifera</i> (grapevine), telmesteine <sup>27</sup> | <ul style="list-style-type: none"> <li>• <b>Hyaluronic acid</b> and <b>shea butter</b> may restore the natural hydration of the skin<sup>27</sup></li> <li>• <b>Glycyrrhetic acid</b> contributes to the emollient's anti-pruritic and anti-inflammatory properties<sup>27</sup></li> <li>• <b><i>Vitis vinifera</i> extract</b> has anti-oxidant and anti-protease activity, which may help protect against the breakdown of epidermal skin<sup>27</sup></li> <li>• <b>Telmesteine</b> exerts anti-elastase and anti-collagenase activity and inhibits metalloproteinases MMP2 and MMP9, which are over-expressed in AD<sup>27</sup></li> </ul>  |
| AtopiControl Body Lotion (Eucerin)             | Glycerol, evening primrose oil, grape seed oil, omega-6 fatty acids, ceramide 3, licochalcone A <sup>28</sup>            | <ul style="list-style-type: none"> <li>• <b>Glycerol</b> acts as a humectant to restore water content and barrier function<sup>24,29</sup></li> <li>• <b>Evening primrose oil</b> and <b>grape seed oil</b> are physiological lipids, which act as substitutes for lost natural skin lipids in the outer layers of the stratum corneum<sup>24,30</sup></li> <li>• <b>Fatty acids</b> help replenish components necessary for skin barrier function<sup>31</sup></li> <li>• <b>Ceramides</b> enhance lipid integration into the skin barrier<sup>26</sup></li> <li>• <b>Licochalcone A</b> has anti-inflammatory effects<sup>32</sup></li> </ul>   |
| Bepanthen Derma (Bepanthen)                    | Dexpanthenol, argan oil, shea butter, squalene, glycerin, niacinamide, and isopropyl isostearate <sup>33</sup>           | <ul style="list-style-type: none"> <li>• <b>Dexpanthenol</b> contributes to barrier function recovery in dry conditions and enhances epidermal differentiation<sup>24,34</sup></li> <li>• <b>Argan oil, shea butter, and squalene</b> are physiological lipids, which act as substitutes for lost natural skin lipids in the outer layers of the stratum corneum<sup>24,30</sup></li> <li>• <b>Glycerin</b> acts as a humectant to restore water content and barrier function<sup>24,29</sup></li> <li>• <b>Niacinamide</b> is an anti-pruritic/soothing agent<sup>35,36</sup></li> <li>• <b>Isopropyl isostearate</b> is a non-physiological lipid, which contributes to normalization of the altered lipid organization/composition in the stratum corneum<sup>24,37</sup></li> </ul> |
| Bepanthen SensiDaily (Bepanthen)               | Panthenol, glycerin, lipids (eg, ceramide 3), vitamin B3, and $\alpha$ -glucan oligosaccharide <sup>38,39</sup>          | <ul style="list-style-type: none"> <li>• <b>Panthenol</b> increases intercellular lipid content and increases length of lipid lamellae<sup>40</sup></li> <li>• <b>Glycerin</b> acts as a humectant to restore water content and barrier function<sup>24,29</sup></li> <li>• <b>Ceramides</b> enhance lipid integration into the skin barrier<sup>26</sup></li> <li>• <b>Vitamin B3</b> increases skin lipid production<sup>26</sup></li> <li>• <b><math>\alpha</math>-glucan oligosaccharide</b> is a prebiotic to normalize skin microbiota<sup>40</sup></li> </ul>  |

(Continued)

Table 1 (Continued).

| Emollient Plus (Company)                                   | Active Substances   | Proposed Mode of Action for AD Treatment   |
|--|---|--|
| Canoderm (ACO HUD Nordic AB)<br>Dermoflan AD (Meda Pharma) | 5% urea <sup>41,42</sup><br><br>Niacinamide, sterols, licorice extract, laureth-9-polydocanol, xylitol, galacto-oligosaccharide <sup>43</sup> | <ul style="list-style-type: none"> <li>• <b>Urea</b> is a humectant that can maintain stratum corneum hydration and enhance TEWL<sup>31</sup></li> <li>• <b>Niacinamide</b> is an anti-pruritic/soothing agent<sup>35,36</sup></li> <li>• <b>Sterols</b> help to restore the skin barrier function<sup>14,16</sup></li> <li>• <b>Licorice extract</b> reduces inflammation<sup>13</sup></li> <li>• <b>Laureth-9-polydocanol</b> reduces itching<sup>20</sup></li> <li>• <b>Xylitol</b> and <b>galacto-oligosaccharide</b> are prebiotics that inhibit the growth of harmful bacteria and promote the growth of beneficial bacteria such as <i>Staphylococcus epidermidis</i>, to maintain the natural skin microbiome<sup>17-19</sup></li> </ul> |
| EpiCeram (Primus Pharmaceuticals)                          | Ceramide, cholesterol, free fatty acids <sup>44</sup>   | <ul style="list-style-type: none"> <li>• A 3:1:1 ratio of <b>ceramides</b>, <b>cholesterol</b>, and <b>free fatty acids</b> is thought to mirror the endogenous intercellular lipid membrane of the stratum corneum and has been shown to repair stratum corneum integrity and function<sup>44</sup></li> </ul>  |
| Eucerin Eczema Relief Body Crème (Eucerin)                 | Colloidal oatmeal, ceramide 3, licochalcone, castor seed oil <sup>45</sup>  | <ul style="list-style-type: none"> <li>• <b>Oatmeal</b> contains several dermatologically active constituents with moisturizing, soothing, anti-inflammatory, barrier protective, and anti-oxidant properties<sup>45</sup></li> <li>• <b>Ceramide 3</b> combats the skin barrier defect, preventing TEWL and dryness<sup>45</sup></li> <li>• <b>Licochalcone</b> has anti-inflammatory effects on the skin, reducing skin irritation, erythema, and itching<sup>45</sup></li> <li>• <b>Castor seed oil</b> contains natural emollients that deeply penetrate the skin, moisturizing the skin and reducing TEWL and dryness<sup>45</sup></li> </ul>   |
| Lipikar Baume AP+ (La Roche-Posay)                         | Niacinamide, shea butter, mannose, biomass of <i>Vitreoscilla filiformis</i> grown in a medium containing thermal spring water <sup>46</sup>  | <ul style="list-style-type: none"> <li>• <b>Niacinamide</b> is an anti-pruritic/soothing agent<sup>35,36</sup></li> <li>• <b>Shea butter</b> fills the cracks between desquamating corneocytes and smoothens the skin<sup>11</sup></li> <li>• <b>Mannose</b> acts as a carbon source to promote the growth of members of <i>Xanthomonadaceae</i> family<sup>46</sup></li> <li>• <b>Vitreoscilla filiformis biomass</b> normalizes skin microbiota<sup>46</sup></li> </ul>  |
| Restoraderm (Galderma Cetaphil)                            | Ceramides, filaggrin breakdown products (arginine and pyrrolidone carboxylic acid), niacinamide <sup>47-49</sup>                              | <ul style="list-style-type: none"> <li>• <b>Ceramides</b> and <b>filaggrin breakdown products</b> help replenish components necessary for skin barrier function<sup>48</sup></li> </ul>  |
| XeraCalm A.D. (Pierre Fabre)                               | Extracts of <i>Aquaphilus dolomiae</i> (l-modulia™) <sup>50,51</sup>  | <ul style="list-style-type: none"> <li>• <b>Niacinamide</b> is an anti-pruritic/soothing agent<sup>35,36</sup></li> <li>• <b>Aquaphilus dolomiae extracts</b> have anti-inflammatory and immunomodulatory effects<sup>50-53</sup></li> </ul>   |

**Abbreviations:** AD: atopic dermatitis; TEWL: transepidermal water loss.

The highest percentage of patients without flare at the end of follow-up was with EC: 99% of patients were flare-free after 4 months of follow-up.<sup>54</sup> A similarly high flare-free rate was with Bepanthen SensiDaily (Bepanthen, Bayer, Green Park, UK) at 96%, although with a shorter follow-up period (3 months). In comparison, use of the reference emollient in the same study (Stelatopia Emollient Cream [Laboratoires Expanscience, Courbevoie, France]) resulted in a flare-free rate of 77%, although this difference was not statistically significant ( $p = 0.083$ ).<sup>38</sup> Treatment with Eucerin Eczema Relief Body Crème plus cleanser and Atoderm Intensive cream (Laboratoire Bioderma, Aix en Provence, France) resulted in flare-free incidences of 79% and 76%, respectively, which, although lower than that of EC and Bepanthen SensiDaily, were reported after longer, 6-month follow-ups.<sup>26,56</sup>

In the studies identified, there was notable variability in the designs, populations, and types of data reported; thus, direct cross-study comparisons are not recommended. Standardization of reporting in emollient plus research may allow

**Table 2** Summary of Studies Reporting Time to Flare and Proportion of Flare-Free Patients for Commercially Available Emollients Plus<sup>†</sup>

| Study                                | Study Population (N)  | Follow-Up Period | Investigative Emollient Plus (n)                                    | Reference/Control Group (n)   | Average Time to Flare, Days |                 |        | Proportion of Patients Without Flare at End of Follow-Up, % |  |                           |
|--------------------------------------|---|------------------|---|---|-----------------------------|-----------------|--------|---|--|---------------------------|
|                                      |   |                  |   |   | Investigative               | Reference       | p      | Investigative   | Reference                                  | p                         |
| Gayraud et al <sup>26</sup>          | Children with AD aged 6 months to 15 years, currently prescribed TCS or TCI (N = 123)   | 6 months         | Atoderm Intensive cream (Laboratoire Bioderma) (n = 62)             | Vehicle (n = 61)  | 59 <sup>‡</sup>             | 39 <sup>‡</sup> | ns     | 76  | 68   | ns                        |
| Angelova-Fischer et al <sup>28</sup> | Adults with mild-to-moderate AD on both arms that had completely resolved with TCS treatment within the last 4 weeks (N = 26)                           | 3 months         | AtopiControl Lotion (Eucerin) (n = 26)                              | Vehicle (n = 26)  | –                           | –               | –      | 68  | 20   | < 0.01                    |
| Stettler et al <sup>38</sup>         | Infants and children aged 1 month to 4 years with acute AD flares, who had achieved disease stabilization with Bepanthen Itch Relief cream (N = 108)    | 3 months         | Bepanthen SensiDaily (Bepanthen) (n = 52)                           | Stelatopia Emollient Cream (Laboratoires Expanscience) (n = 56)                             | 47 <sup>‡</sup>             | 50 <sup>‡</sup> | –      | 96  | 77   | 0.083                     |
| Wirén et al <sup>42</sup>            | Adults with AD, who had successful clearing of their atopic lesions after 3 weeks of topical BMV 0.1% (N = 44)  | 6 months         | Canoderm Cream 5% (n = 22)  | Untreated (n = 22)  | >180 <sup>§</sup>           | 30 <sup>§</sup> | 0.01   | 32  | 68   | –                         |
| Åkerström et al <sup>41</sup>        | Adults with AD, who had achieved stabilization with topical mometasone furoate 0.1% and/or hydrocortisone 1%, plus Miniderm with 20% glycerol (N = 172) | 6 months         | Canoderm Cream 5% (n = 87)  | Miniderm without glycerol (n = 85)  | 22 <sup>§</sup>             | 15 <sup>§</sup> | 0.013  | 26  | 10   | –                         |
| Sparavigna et al 2020 <sup>54</sup>  | Patients aged >12 years with mild-to-moderate AD, who had responded successfully to pimecrolimus 1% (N = 101)   | 4 months         | Dermoflan AD (Meda Pharma) (n = 101)                                | N/A   | –                           | –               | –      | 99  | –  | –                         |
| Tiplica et al <sup>55</sup>          | Children (aged 2–6 years) with mild-to-moderate AD, who had responded successfully to desonide 0.1% (N = 335)   | 3 months         | Dexeryl (Pierre Fabre) (n = 111)                                    | Atopiclair (Sinclair Pharma) (n = 116) or no emollient (n = 108)                            | –                           | –               | –      | 60  | 44 (reference emollient) 30 (no emollient) | < 0.001 (vs no emollient) |
| Weber et al <sup>56</sup>            | Infants and children (aged 3 months to 12 years) with AD (N = 45)   | 6 months         | Eucerin Eczema Relief Body Crème (Eucerin) with cleanser (n=21)     | Cleanser only (n = 24)  | >180 <sup>§</sup>           | 28 <sup>§</sup> | < 0.05 | 79  | 35   | –                         |
| Seité et al <sup>46</sup>            | Patients aged 6 months to 63 years with moderate AD, who had been pretreated with TCS, immunosuppressive therapy, or phototherapy (N = 53)              | 1 month          | Lipikar Baume AP+ (La Roche-Posay) (n = 26)                         | Commercial AD product containing triglyceride, glycerin, shea butter, and ceramide (n = 27) | –                           | –               | –      | 65  | 33   | –                         |
| Ma et al <sup>49</sup>               | Children aged 2–12 years with mild-to-moderate AD, who had been successfully treated with TCS within the last week (N = 64)                             | 3 months         | Restoraderm moisturizer with body wash (Galderma Cetaphil) (n = 32) | Body wash only (n = 32)   | 89 <sup>§</sup>             | 27 <sup>§</sup> | –      | 50  | 28   | –                         |

**Notes:** <sup>†</sup>This table is intended as a summary of key studies and is not intended for cross-study comparisons. Cross-study comparisons should not be carried out as studies are performed under different conditions, with different study designs and in different patient populations, and data reported may not be consistent. <sup>‡</sup>Mean. <sup>§</sup>Median.

**Abbreviations:** AD, atopic dermatitis; BMV, betamethasone valerate; N/A, not applicable; ns, not significant; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

stronger conclusions to be drawn regarding efficacy. It should also be noted that this narrative review did not employ systematic review methodology; the publications listed may not represent an exhaustive list of available studies.

## Skin Barrier Function in AD Pathogenesis

The clinical efficacy of an emollient plus, as summarized above, may be determined by its ability to restore and maintain skin barrier function. The inflammatory, biochemical, microbial, and neurosensory changes seen in AD pathogenesis are described below.<sup>7</sup>

The inflammatory cascade in AD has been extensively reviewed.<sup>57,58</sup> In brief, antigen penetration through damaged skin and presentation by antigen-presenting cells leads to a Th2 response, resulting in immunoglobulin E production. This can lead to degranulation of mast cells, a local inflammatory response, and recruitment of other inflammatory cells, such as eosinophils. Langerhans cells and inflammatory dendritic cells, activated by pathogen-derived antigens, promote Th1- and Th2-driven immune responses in acute AD lesions. However, as the understanding of the genetic contribution to AD has improved, the pathophysiology of AD is now recognized as being driven by an impaired skin barrier, rather than a purely immunological disorder.<sup>1,59</sup>

There is also evidence to suggest that skin pH regulation may be overlooked in AD disease pathogenesis. AD lesions have higher pH values than healthy skin,<sup>60</sup> and a positive correlation was observed between severity of itch in children with AD and higher skin pH.<sup>61</sup> This is supported by a phenome-wide association study that demonstrated a statistically significant association between AD and a single-nucleotide polymorphism (SNP) in G protein-coupled receptor (GPR) 65.<sup>62</sup> GPR65 is an extracellular pH-sensing receptor widely expressed on immune cells.<sup>63</sup> Normal signaling through GPR65 at low pH inhibits inflammatory cytokine release from immune cells;<sup>64,65</sup> the SNP in AD reduces GPR65 signaling.<sup>62</sup> Furthermore, GPR65 deficiency in a murine AD model resulted in exacerbated disease,<sup>62</sup> demonstrating a mechanism by which the AD inflammatory cascade may be linked to skin pH.

The skin microbiome and presence of pathogens such as *Staphylococcus aureus* have also been implicated in AD pathogenesis.<sup>66</sup> In healthy skin, the microbiome protects against colonization by pathogenic microbes via secretion of anti-microbial peptides and free fatty acids.<sup>66</sup> However, in AD, the microbial community structure at sites of disease predilection is different compared with healthy controls. A correlation exists between decreased microbial diversity and increased severity of AD.<sup>67</sup>

Maintaining skin barrier integrity is central to AD management, and the capacity for treatment to restore and/or maintain skin barrier function as discussed above may be beneficial.

## The Efficacy of Emollients Plus on Maintaining and Restoring the Skin Barrier

Below, we highlight recent evidence from pre-clinical and clinical studies for the capacity of emollients plus to restore barrier function at the physical and biochemical, microbial, immunological, and neurosensory levels of the skin barrier.

### The Physical and Biochemical Barriers

The physical skin barrier consists of corneocytes, desmosomes, claudins and lipids, while the biochemical barrier is composed of molecules that contribute to hydration (eg, natural moisturizing factors) and prevention of infections (eg, anti-microbial peptides).<sup>7</sup>

In a recent in vitro study by Quadri et al, skin organ cultures were subject to tape stripping (100 repeated applications and subsequent removals of adhesive tapes to the skin surface) as a model for skin barrier damage. After incubation with either 100% or 50% EC solution or diluent alone, skin barrier recovery was assessed.<sup>43</sup> Tape stripping resulted in complete removal of the epidermal stratum corneum and intercellular lipid component. Following culture with EC, epidermal thickness was significantly increased in organ cultures treated with 100% EC solution compared with those treated with diluent alone ( $p < 0.01$ ).<sup>43</sup> The application of 50% or 100% EC significantly increased lipid detection after only 24 hours compared with diluent, and after 120 hours restored lipid content to 99% and 93%, respectively, of that in unstripped tissue.<sup>43</sup>

Additionally, skin barrier restoration after tape stripping was assessed through expression of involucrin and caspase-14 (differentiation markers), claudin-1 (a tight junction protein normally homogeneously expressed in the stratum

granulosum), and keratin-16 (an intermediate filament cytoskeletal protein expressed in keratinocytes in response to epidermal barrier challenges).<sup>43</sup> Compared with diluent, claudin-1 expression was significantly increased with both 50% and 100% EC solution ( $p < 0.05$  and  $p < 0.01$ , respectively), involucrin expression was significantly increased with 100% EC only ( $p < 0.05$ ), and caspase-14 expression was significantly increased with both 50% and 100% EC ( $p < 0.01$  for both). Keratin-16 expression was significantly reduced with 100% EC only ( $p < 0.05$ ) compared with diluent.<sup>43</sup>

A clinical study was performed to validate these findings. Patients with mild-to-moderate AD in clinical remission ( $N = 20$ ) applied EC ( $n = 10$ ) or placebo ( $n = 10$ ) once a day for 2 consecutive months in the antecubital folds of the upper and lower limbs. Once-daily EC application reduced vascularization and epidermal thickness, and increased skin hydration in patients with mild-to-moderate AD in clinical remission, thus validating the in vitro findings, albeit with a small sample of patients.<sup>43</sup>

In a 2019 clinical study, 60 patients with mild AD applied EC or vehicle twice daily on their forearms for 28 days.<sup>68</sup> Skin hydration, as measured by corneometry, was significantly improved by 19% after 28 days in patients treated with EC versus baseline ( $p < 0.05$ ). Skin desquamation was also significantly decreased in patients treated with EC at the 14-day and 28-day timepoints, compared with baseline ( $p < 0.05$ ). Skin barrier function, measured by TEWL, was significantly improved by 17% after 28 days in patients treated with EC versus baseline ( $p < 0.05$ ). There was also a significant difference in skin hydration between the EC-treated and vehicle-treated groups at each timepoint ( $p < 0.05$ ).

The capacity for EC to increase skin moisture levels and decrease TEWL was also shown in a small clinical study by Gasparri et al. In adults with AD ( $N = 10$ ), skin moisture levels in treated areas were significantly higher at day 21 compared with baseline: mean skin moisture increased from baseline by 115.5% (corneometric units: 27.7 vs 13.1, respectively;  $p < 0.001$ ), and TEWL was significantly reduced.<sup>69</sup>

## The Microbial Barrier

Microbes contribute to the skin barrier by producing anti-microbial peptides and free fatty acids, and stimulating the innate immune system.<sup>7</sup> *Staphylococcus aureus* colonization is a critical driver of AD inflammation.<sup>70</sup> A study by Kong et al demonstrated that microbial diversity during AD flares depends on recent AD treatments, with even intermittent treatment (use of topical calcineurin inhibitors [TCI]/topical corticosteroids [TCS]/antibiotics in the past 7 days and/or consumption of oral antibiotics within 4 weeks before sampling) linked to reduction in *Staphylococcus aureus* and greater bacterial diversity compared with no recent treatment.<sup>67</sup>

Supporting these findings, *Staphylococcus aureus* growth and biofilm formation were assessed in vitro. EC rapidly (<3 hours) inhibited the growth and biofilm formation of two strains of *Staphylococcus aureus*.<sup>15</sup> In clinical validation, patients predisposed to AD ( $N = 11$ ) applied EC twice daily between the neck and shoulders. Microbial diversity significantly increased in EC-treated areas at day 28 versus baseline ( $p = 0.037$ ).<sup>15</sup>

The microbiome maintenance action of EC is thought to be driven by the active ingredients galacto-oligosaccharides and xylitol. Galacto-oligosaccharides are a group of prebiotics.<sup>17</sup> Prebiotics may promote the growth of beneficial commensal bacteria (eg, *Staphylococcus epidermidis*), thus preventing colonization by pathogenic bacteria (eg, *Staphylococcus aureus*).<sup>19,71</sup> Xylitol has been shown to inhibit the formation of glycocalyx, a component of *Staphylococcus aureus*-associated biofilm.<sup>18</sup>

There is evidence for the capacity of another emollient plus, Lipikar Baume AP+ (La Roche-Posay, London, UK), in normalization of the skin microbiome.<sup>72</sup> In a single-center study in patients with moderate AD ( $N = 49$ ), patients applied Lipikar Baume AP+ twice daily to their entire body. Twice-daily application of Lipikar Baume AP+ improved symptoms in over 70% of patients and was associated with increased bacterial diversity and decreased *Staphylococcus* species. The abundance of *Staphylococcus* species was inversely related to microbial diversity.<sup>46,73</sup>

## The Immunological Barrier

The immunological barrier involves components of the innate immune system (eg, anti-microbial peptides produced by keratinocytes) and the adaptive immune system (eg, dendritic cells and lymphocytes).<sup>7</sup> Toll-like receptors (TLRs) are thought to play a role in AD susceptibility, and increased susceptibility to microbial infections in patients with AD may be attributed to TLR functional abnormalities.<sup>74</sup> EC treatment is associated with increased expression of TLR-1 and TLR-2,<sup>43</sup> indicating that EC may support the epidermal defense against pathogens.

Another emollient plus compound, I-modulia (Pierre Fabre, Paris, France), an *Aquaphilus dolomiae* extract, has demonstrated anti-inflammatory and immunomodulatory effects. In vitro, I-modulia regulated keratinocyte inflammatory and lymphocyte immune responses, including thymic stromal lymphopoietin, interleukin (IL)-18, IL-4R, IL-8, monocyte chemoattractant protein-3, macrophage inflammatory protein-3a, and macrophage-derived chemokine.<sup>51,52</sup> I-modulia has been suggested to activate TLR-2, TLR-4, and TLR-5, and subsequently induce anti-microbial peptides via TLR-5.<sup>53</sup> I-modulia also displayed inhibition of human mast cell degranulation in vitro.<sup>50</sup>

### The Neurosensory Barrier

Components of the neurosensory system function as sensors of external stimuli and include keratinocytes and ion channels expressed on cutaneous nerves. When activated, sensory nerve endings release neuropeptides such as substance P, mediating itch, pain, and inflammation.<sup>7</sup> This is further compounded by the itch-scratch cycle: pruritus compels a patient to scratch AD lesions, resulting in a short-term neurological reward response but stimulating further dermatological inflammation.<sup>75,76</sup>

In the 2019 clinical study, in which 60 patients with mild AD used EC or vehicle twice daily on their forearms for 28 days, pruritus was significantly reduced by 89% in patients treated with EC versus baseline ( $p < 0.05$ ).<sup>68</sup> Patient self-evaluation showed a reduction in pruritus after just 4 days treatment with EC versus vehicle, which continued steadily and progressively. Desquamation was significantly reduced by 83% after 28 days in patients treated with EC versus baseline ( $p < 0.05$ ), although there was no significant difference in desquamation between the EC- and vehicle-treated groups at any timepoint.

The capacity for EC to improve desquamation and decrease itching was shown in a small clinical study: in adults with AD ( $N = 10$ ), desquamation in treated areas significantly improved from moderate at baseline (mean rating 3.1) to largely absent by day 7 (mean rating 1.1 at days 7 and 21;  $p < 0.005$  vs baseline at all time points). Most (9/10) patients reported improvements in itching after 24 hours.<sup>69</sup>

## AD Topical Treatment Approaches: Guidelines and Supporting Evidence

The European guidelines for AD treatment recommend liberal and frequent use of emollients (minimum amount of 250 g per week for adults), and the American Academy of Dermatology advises that moisturizers should be the primary treatment for mild disease and part of the regimen for moderate/severe disease.<sup>6,77</sup> A recently published algorithm to inform clinical decision-making recommends regular use of emollients for early AD control.<sup>78</sup> However, the European guidelines note that direct sole use of emollients on inflamed skin is poorly tolerated, and so induction of remission with TCS or TCI is required before application of the emollient.<sup>6</sup>

For long-term AD management, an alternative to TCS is required;<sup>79</sup> prolonged use of TCS can cause skin atrophy, barrier impairment, increased infection risk, and tachyphylaxis.<sup>6,80–82</sup> Additionally, corticophobia is an issue in patients receiving TCS: over 80% of patients and caregivers have concerns about TCS and 36% of patients are nonadherent to TCS treatment.<sup>83</sup>

TCI, namely pimecrolimus and tacrolimus, are favorable over TCS for topical long-term management as they do not impair the epidermal barrier function or cause skin atrophy.<sup>6,84</sup> In an evaluation of a pimecrolimus-based regimen in patients at least 3 months old, a high percentage of patients were clear or almost clear of AD signs at the end of treatment.<sup>85</sup> Pimecrolimus treatment also reduced TCS use: 47% of patients never used TCS over the 6-month study period, indicating that pimecrolimus has a steroid-sparing effect.<sup>85</sup> Pimecrolimus has an improved safety profile versus TCS, with lower systemic exposure.<sup>86</sup> Although the JOELLE study reported a possible increased risk of lymphoma with tacrolimus and pimecrolimus, the low incidence rates implied that even if the increased risk is causal, it represents a small excess risk for individual patients. Residual confounding by AD severity, increased monitoring of severe patients, and reverse causation could have affected the results.<sup>87</sup> Previous reports have found no evidence to suggest an increased risk of lymphoma with TCI.<sup>79,88,89</sup>

Regular emollient use may decrease the need for TCS while maintaining efficacy in AD treatment.<sup>90–92</sup> In 108 children with moderate AD (aged 6 months to 6 years) treated with an oat-based sterile emollient plus cream for 3 months, the number of flares and use of TCS significantly decreased by month 3 (both  $p < 0.001$ ).<sup>93</sup> Additionally, in 2456



patients with mild-to-moderate AD treated with an emollient plus containing N-palmitoylethanolamine, TCS were omitted by 56% of patients at the end of the study. The average weekly application rate of TCS decreased by 62% from  $7.9 \pm 6.0$  to  $3.0 \pm 5.1$  ( $p < 0.001$ ).<sup>94</sup>

Compared with other topical therapies, emollients are rarely associated with health hazards, even when used on large body surface areas over an extended period.<sup>31</sup> Some emollients may cause contact irritation, although this is rare. Specific emollient components require extra attention regarding safety: occlusive oils are associated with cosmetic acne, while preservatives such as sorbic acid, fragrances, or balsam of Peru may cause contact urticaria.<sup>31</sup>

With regard to emollients plus specifically, tolerability is generally good with few adverse events (AEs) reported. One study investigating an emollient plus containing vitamin B3, palmitoyl ethanolamide,  $\beta$ -sitosterol, zinc, and ceramides reported that 4/62 patients (6.5%) experienced symptoms possibly or definitely related to treatment, including warm sensation, pruritus, stinging, pain, erythema, and flare-ups.<sup>26</sup> Another study reporting on an emollient plus containing 5% urea reported that 5/87 patients (6%) experienced at least one treatment-related adverse event (TRAE) and one patient experienced a severe TRAE.<sup>41</sup> Three further studies investigating different emollients plus (including a panthenol-containing emollient plus, a niacinamide-containing emollient plus, and a ceramide 3-containing emollient plus) all reported good tolerability with no AEs related to treatment.<sup>38,49,56</sup>

With EC to date, no AEs have been reported in patients with AD.<sup>43,54,68</sup> In one study, investigators judged EC tolerability as good or excellent in 100% of treated patients.<sup>54</sup> In a patient assessment of EC, the majority of patients rated EC as good or excellent in terms of cosmetic acceptability.<sup>68</sup>

Safety implications must be considered when selecting an AD topical treatment approach. Various emollient treatment approaches have been recommended: from prophylactic use in neonates and infants to prevent AD occurrence, to proactive, intermittent, and synergistic treatments.

## The Preventative Approach

### Emollients for the Prevention of AD

Evidence suggests that prophylactic use of emollients can prevent AD flares. In a study evaluating a body wash and moisturizer regimen (Cetaphil Restoraderm Skin Restoring Body Wash and Cetaphil Restoraderm Skin Restoring Moisturizer [Galderma Laboratories, L.P., Fort Worth, USA]) for infants and toddlers (aged 3–36 months) with a history of AD ( $N = 56$ ), the percentage of subjects with no erythema increased from 33.9% to 50.0% by week 4.<sup>47</sup> The percentage of subjects with no scaling/dryness increased from 58.9% to 85.2% at week 4.

In a randomized controlled trial in 124 neonates at high risk for AD, Simpson et al investigated whether skin barrier enhancement with emollients (an oil, cream/gel, or ointment) from birth represents a feasible strategy for reducing AD incidence.<sup>95</sup> Daily emollient use significantly reduced the cumulative incidence of AD at 6 months (43% vs 22% for control vs emollient, respectively), with a relative risk (RR) reduction of 50% (RR: 0.50; 95% confidence interval [CI]: 0.28–0.90;  $p = 0.017$ ).

This is supported by a study by Horimukai et al: daily application of an emulsion-type emollient (2e [Douhet] emulsion) during the first 32 weeks of life reduced AD risk in infants considered to be at high risk for the condition ( $N = 118$ ).<sup>96</sup> Approximately 32% fewer neonates who received the emollient had AD by week 32 compared with control subjects ( $p = 0.012$ ). In 100 neonates (recruited as newborns within 21 days), McClanahan et al also found a trend for a protective effect of daily Restoraderm moisturizer full-body application compared with application of control emollient to dry skin only. A trend for reduced AD incidence was observed with Restoraderm moisturizer compared with control at 12 months (13.2% vs 25.0%, respectively;  $p = 0.204$ ) and 2 years (19.4% vs 31.0%, respectively;  $p = 0.296$ ), but did not reach statistical significance.<sup>97</sup>

However, there is conflicting evidence on the preventative use of emollients for AD. In the Barrier Enhancement for Eczema Prevention (BEEP) multicenter, randomized, controlled trial, 1394 newborns at high risk of developing AD were assigned to receive either daily emollient (either Diprobace cream [Bayer, Barmen, Germany] or DoubleBase gel [Dermal Laboratories Ltd., Hitchin, UK]) or control for the first year of life.<sup>98</sup> At two years of age, AD was present in 23% of infants in the emollient group and 25% of infants in the control group (adjusted RR: 0.95 [95% CI: 0.78–1.16],  $p = 0.61$ ; adjusted risk difference  $-1.2\%$  [95% CI:  $-5.9$  to  $3.6$ ]), suggesting that daily emollient use during the first year of life does

not prevent AD in high-risk children. There was also evidence to suggest that daily emollient use in the first year of life may increase infection risk.

### Emollients for the Prevention of Atopic March

The ‘atopic march’ is a clinical sequence that begins with AD and progresses to food allergy followed by development of respiratory allergies, such as asthma and allergic rhinitis.<sup>99</sup> It remains unclear whether regular emollient application to the skin of neonates can decrease the risk of AD progression to food allergies.<sup>99</sup> The ‘Prevention of AD By a Barrier Lipid Equilibrium Strategy’ (PEBBLES) pilot study showed a trend for decreased food sensitization at 6 and 12 months of age when emollients were used preventatively from birth, particularly when the lipid-rich emollient was introduced early (<2 weeks after birth) and used frequently ( $\geq 5$  days per week). However, this study was not powered to detect differences or measure true food allergy outcomes.<sup>100</sup>

Conversely, in the BEEP trial, food allergies to milk, egg, or peanut were confirmed in 7% of infants in the emollient group and 5% in the control group (adjusted RR: 1.47; 95% CI: 0.93–2.33), and the proportion of infants with allergic rhinitis, wheezing, and allergic sensitization to cat dander, grass pollen, and dust mites was similar between groups.<sup>98</sup> The Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) trial aimed to determine if either regular emollient application from 2 weeks of age, or early complementary feeding introduced between 12 and 16 weeks of age, reduced AD development by 12 months in the general population (N = 2397). Neither emollients nor early complementary feeding reduced AD development, with a risk difference of 3.1% (95% CI: –0.3 to 6.5) for skin intervention and 1.0% (95% CI: –2.1 to 4.1) for food intervention, in favor of control.<sup>101</sup>

Evidence for the use of emollients in the prevention of AD and atopic march is conflicting. This is perhaps unsurprising given the heterogeneous compositions of commercially available emollients (Table 1); it is possible that the specific composition of different emollients and/or emollients plus can impact their effects.

In the BEEP trial, participants could choose between Doublebase Gel or Diprobase Cream. Doublebase Gel is composed of two emollients: isopropyl myristate and liquid paraffin.<sup>102</sup> There are a range of creams in the Diprobase range with differing compositions, and it is not clear which was used in the BEEP trial. In the PreventADALL trial, the skin intervention consisted of baths with emulsified oil (paraffinum liquidum and trilaureth-4-phosphate) and Ceridal cream (GSK, London, UK), whose key ingredients are petrolatum, paraffinum liquidum, and glycerin.<sup>103</sup> The emollients used in the BEEP and PreventADALL trials were not emollients plus containing additional active ingredients. Hypothetically, an emollient plus may be more effective at preventing AD and atopic march; prospective trials are required to confirm this hypothesis.

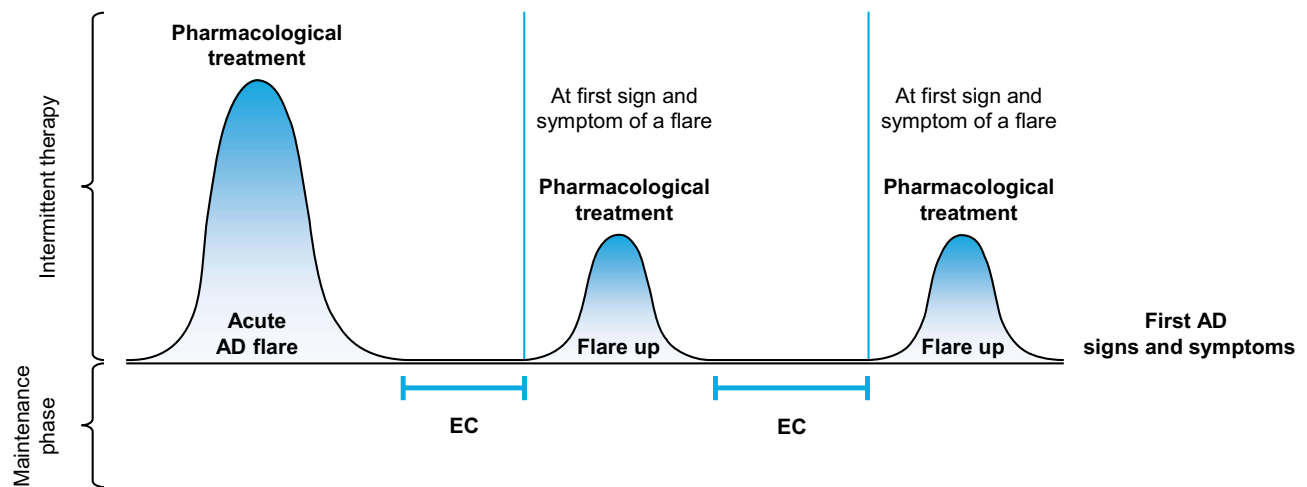
In future AD studies, the choice of emollient or emollient plus (and its composition) should be carefully considered. Publications should not only incorporate transparent reporting of the choice of emollient or emollient plus, but also discuss the impact of any active ingredients on results. Head-to-head trials are required to determine the most effective composition for emollients plus.

### The Proactive Approach

For established disease, a proactive approach to long-term AD management has been suggested, where flares are treated with anti-inflammatory therapy (TCI or TCS) until the affected areas are almost clear.<sup>104</sup> Anti-inflammatory treatment on previously affected skin areas should subsequently continue once or twice per week (depending on disease severity) in combination with an emollient, regardless of AD signs or symptoms.<sup>6,105</sup> Tacrolimus 0.03% twice daily for treatment of flares for a maximum of 6 weeks, followed by proactive use of tacrolimus 0.03% twice weekly to all affected areas for 1 year was shown to increase median time to flare from 36 days in the vehicle control group to 217 days in the proactive tacrolimus group.<sup>106</sup>

### The Intermittent Approach

Conversely, an intermittent approach to long-term AD management involves applying TCS or TCI at the first signs (ie, erythema) or symptoms (ie, pruritus) of AD to prevent progression to flare. This was trialed in a study where 713 patients with AD (aged 2–17 years) were randomized to either a pimecrolimus-based regimen (emollients with pimecrolimus at the first early signs and symptoms of flare) or a conventional regimen (emollients with vehicle at the first early signs and symptoms of flare). Intermittent use of pimecrolimus was associated with a significantly longer flare-free period



**Figure 1** The synergistic approach to long-term AD management. Figure developed as a result of the expert panel's discussions, in line with treatment labels and previous data.<sup>54,108</sup>

**Abbreviations:** AD, atopic dermatitis; EC, emollient cream.

compared with the conventional regimen ( $p < 0.001$ ). The proportion of patients with no flares after 6 and 12 months was approximately twice as high in the group treated with pimecrolimus plus emollient compared with those treated with emollient alone (61.0% vs 34.2%, respectively, at 6 months; 50.8% vs 28.3%, respectively, at 12 months).<sup>107</sup>

### The Synergistic Approach

In an open-label, multi-center study on EC use for maintaining disease regression after pimecrolimus therapy in mild-to-moderate AD, EC after pimecrolimus maintained regression of flare for at least 4 months in almost all patients: 98% of patients at the end of the study were clear or almost clear of signs and symptoms at 4 months.<sup>54</sup> Improvement was observed in all other efficacy outcomes, including Investigator's Global Assessment, SCORing Atopic Dermatitis, and Visual Analog Scale.<sup>54</sup> A synergistic approach, with pharmacological intervention for flare treatment and emollient cream for maintenance therapy, may be useful in management of mild-to-moderate AD, as illustrated in Figure 1. Using pimecrolimus and EC, this approach allows patients to avoid the use of rescue medication (topical anti-inflammatory treatment) for up to 4 months.<sup>54</sup>

## Conclusion

Based on the evidence summarized in this review, the authors recommend the novel generation of emollients, emollients plus, for AD maintenance therapy. However, not all emollients plus are created equal: their composition can vary widely with a profound impact on clinical efficacy. This should not be overlooked when interpreting results. Despite a wealth of evidence supporting the clinical efficacy of emollients plus in AD and their ability to restore and maintain skin barrier function, head-to-head trials are required to determine their most effective composition for AD treatment.

When considering AD treatment, the safety profiles of topical therapies must be carefully examined. There are data to support several treatment approaches for emollients in AD, including preventative, proactive, intermittent, and synergistic approaches. Although there is conflicting evidence on the use of emollients for preventing atopic march, regular, synergistic use of emollients is effective for AD disease control and reduces the need for anti-inflammatory treatment. This reduces the risk of adverse reactions associated with TCS.

The ability of emollients plus to repair and maintain the skin barrier places them not only as suitable maintenance therapies for AD, but also as effective treatment options when used synergistically with anti-inflammatory pharmacological therapies.

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