The Evolving Role of Biologics in the Treatment of Pediatric Psoriasis

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ABSTRACT
The exact role of biologics in the treatment of pediatric psoriasis remains undefined but is evolving. Biologics are an attractive option for use in children in part because they offer more convenient dosing regimens and less frequent laboratory monitoring than traditional systemic agents. Further, because their action is targeted, they theoretically lack many of the potential end-organ toxicities of traditional agents. However, compared to adult psoriasis populations, there is a relative lack of long-term safety data specific to the pediatric psoriasis population. Thus, the clear advantages of using biologic agents must be balanced with a measure of caution. This article will provide a summary of the cumulative pediatric safety and efficacy data for the anti-tumor necrosis factor-alpha (TNF-α) agents and interleukin (IL)-12 and IL-23 (IL12/23) pathway inhibitor and suggestions for a rational clinical approach to their use in children with psoriasis.

Key words: biologic agents, childhood, pediatric psoriasis

Illustrative Case
An 8-year old boy was admitted to the hospital with a severe flare of generalized pustular psoriasis covering 100% of his body surface area. Prior to admission, he had failed aggressive topical therapy as well as systemic therapy with acitretin 1 mg/kg/day and cyclosporine 5 mg/kg/day. His disease was rapidly progressive and at the time of admission he had significant electrolyte imbalance as well as systemic symptoms including fevers, chills, arthralgias, malaise, and skin pain. What are the treatment options in this case?

Discussion
The Role of Biologics in Pediatric Psoriasis
In the past decade, biologics have gained a prominent role in the treatment of moderate to severe psoriasis in the adult population. The efficacy of the currently approved agents for psoriasis in adults, which includes anti-tumor necrosis factor-alpha (TNF-α) inhibitors and an interleukin (IL)-12 and IL-23 (IL12/23) pathway inhibitor, is supported by multiple randomized controlled studies, with newer agents continuing to surface in the development pipeline. The exact role of biologics in the treatment of pediatric psoriasis remains relatively undefined. Biologics are convenient to use, requiring less frequent dosing and laboratory monitoring than traditional systemic agents such as methotrexate, cyclosporine, and acitretin. In addition, because their action is targeted, they theoretically lack many of the potential end-organ toxicities of traditional agents. For these reasons, biologics are an attractive option for treating psoriasis in children. The clear advantages of using biologic agents, however, must be balanced with a measure of caution. Compared to adult psoriasis populations, there is a relative lack of long-term safety data specifically in pediatric psoriasis, more so for IL12/23 inhibitors than anti-TNF-α agents, to confidently prescribe them routinely as first-line agents. High cost often factors prominently in the ability of patients to receive these medications, as lack of US FDA approval for the treatment of psoriasis in patients less than 18 years of age can create obstacles when obtaining insurance coverage for first-line use. Practically, administration by injection or infusion can be a deterrent for some children. Thus, while the science, derived largely from studies in adults, suggests that biologic agents should be effective and well tolerated in the pediatric population, the art in managing pediatric psoriasis lies in balancing the attractive short-term benefits against the barriers to their use, including cost, coverage issues, administration requirements, and unknown potential risks of long-term use in children with psoriasis.

Dosing and Monitoring
Because of the paucity of available data, no formal guidelines exist for dosing and laboratory monitoring of children while on biologic therapy for psoriasis. At this time, there has been only one randomized double-blind trial published in the literature; all other data derives from case series and case reports. In general, children should undergo baseline tuberculosis screening, immunization updates, and laboratory studies prior to drug therapy.
initiation, followed by routine (every 4-6 months) laboratory monitoring and close clinical surveillance (every 2-3 months) for adverse events, particularly infections (see Table 1). These suggestions may be modified in individual cases.

### Anti-Tumor Necrosis Factor-alpha Agents

**Etanercept (Enbrel<sup>®</sup>)**

Of all the currently available biologics, etanercept has accumulated the most evidence for efficacy and safety in the pediatric population, including pediatric psoriasis. Etanercept is a TNF receptor-IgG fusion molecule that inhibits TNF-α. The best data for efficacy in pediatric psoriasis comes from a phase III double-blind randomized controlled trial comparing etanercept 0.8 mg/kg weekly to placebo in 211 patients aged 4-16 years with moderate to severe plaque psoriasis over 48 weeks. No deaths, cancers, opportunistic infections, tuberculosis, or demyelination events were reported in the study. Data at the 96-week point of the ongoing 264-week open-label extension of the study showed continued efficacy, tolerability, and safety of etanercept in 140 patients. The most common adverse events during this period were minor infections such as upper respiratory tract infections and pharyngitis, injection site reactions, and headaches. Severe infections, including gastroenteritis-related dehydration and lobar pneumonia, were rare and their relationship to the drug questionable. Published case reports indicate success in treating erythrodermic, generalized pustular, and palmoplantar psoriasis in patients ranging in age from 22 months to 17 years. Based on the efficacy and safety data reported thus far, in 2009 the European Commission approved the use of etanercept for treatment of children aged 6 and older with chronic severe plaque psoriasis refractory to, or intolerant of, other systemic therapies or phototherapy.

Much of the long-term safety data for etanercept is derived from its use in juvenile idiopathic arthritis (JIA; formerly referred to as polyarticular juvenile rheumatoid arthritis), for which etanercept was approved in 1999. Although comparing safety of drugs in different disease populations is not ideal, the long-term use of etanercept in JIA helps to substantiate recommendations for its use in pediatric psoriasis. One study in JIA patients with 8 years of follow-up data found a rate of serious adverse events of 0.12 per patient-year, which did not increase with length of exposure, and a rate of serious infections at 0.03 per patient-year. Studies in JIA have reported non-demyelinating neuropathy, varicella with aseptic meningitis, and sepsis. There have been no opportunistic infections, malignancies, demyelinating disorders, or deaths in combined data for JIA. Considering the quality and quantity of the data for pediatric psoriasis in addition to long-term safety data in other diseases, etanercept should be considered for use among other first-line traditional systemic agents in cases of severe or refractory plaque, erythrodermic, and pustular psoriasis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Miscellaneous</th>
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</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>0.8 mg/kg subcutaneous injection weekly</td>
<td>• PPD</td>
<td>• PPD annually</td>
<td>• Update vaccinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Electrolytes</td>
<td>• CBC</td>
<td>• Avoid live and live-attenuated vaccines (e.g., varicella, MMR, oral typhoid, yellow fever, intranasal influenza, herpes zoster, BCG)</td>
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<tr>
<td></td>
<td></td>
<td>• Liver function</td>
<td>• Liver function every 4-6 months</td>
<td>• Vaccinate household contacts prior to treatment initiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CBC with differential</td>
<td>• Liver function more frequently with infliximab</td>
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<tr>
<td></td>
<td></td>
<td>• Hepatitis A/B/C if at risk</td>
<td>• Other labs and serologies per individual signs and symptoms</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• HIV if at risk</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Others per individual situations</td>
<td></td>
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<tr>
<td>Infliximab</td>
<td>3.3-5 mg/kg intravenous infusion at weeks 0, 2, 6, then every 7-8 weeks</td>
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<tr>
<td>Adalimumab</td>
<td>24 mg/m² subcutaneous injection (max. 40 mg) every 2 weeks*</td>
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<tr>
<td>Ustekinumab</td>
<td>Not specified: single case report of 45 mg at weeks 0, 4, then every 12 weeks**</td>
<td>• PPD, no other specific recommendations, likely similar to other biologic agents</td>
<td>• PPD annually, no other specific recommendations, likely similar to other biologic agents</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1: Recommendations for dosing and monitoring for pediatric psoriasis**


CBC = complete blood count; PPD = purified protein derivative; MMR = measles mumps rubella vaccine; BCG = Bacillus Calmette-Guérin

* Dosing from published experience in patients with juvenile idiopathic arthritis; in two case reports of pediatric psoriasis, dosing was 40 mg every 2 weeks in two adolescent patients

** Dosing from single case report; adult dosing is either 45 mg or 90 mg at weeks 0, 4, and then every 12 weeks depending on weight

*** Dosing reported from CADMUS study currently evaluating two doses of ustekinumab vs. methotrexate. Low dose ustekinumab is 0.375 mg/kg for <60 kg or fixed doses of 22.5 mg or 45 mg based on weight at weeks 0 and 4 then every 12 weeks. High dose ustekinumab is 0.75 mg/kg for <60 kg or fixed doses of 45 mg or 90 mg based on weight at weeks 0 and 4 then every 12 weeks.
**Infliximab (Remicade®)**

Infliximab was FDA approved in 2006 for the treatment of Crohn’s disease in children aged 6 years and older. Infliximab is a chimeric monoclonal antibody with potent activity against TNF-α, although its documented use in pediatric psoriasis is limited to case reports and anecdotal experience. When used for refractory plaque and generalized pustular psoriasis in children, it has been observed to be uniformly effective at doses of 3.3 to 5 mg/kg administered at weeks 0, 2, 6, and every 7-8 weeks thereafter. Time to onset of effect has been as rapid as hours to days.\(^{21-25}\)

In comparison with etanercept, patients receiving infliximab for JIA were found to have frequent and more serious adverse events.\(^{26,27}\) In adult psoriasis patients, infliximab is reported to carry an increased risk of tuberculosis reactivation and congestive heart failure.\(^{28}\) Sporadic use of infliximab should generally be avoided as it may increase the induction of neutralizing antibodies against the murine portion of the molecule, thus leading to decreased efficacy and increased risk of transfusion reactions.\(^{29}\) Of note, the addition of an additional immunosuppressant in order to reduce formation of anti-chimeric antibodies has been linked to rare cases of potentially fatal hepatosplenic T-cell lymphoma. To date, this association has only been observed in pediatric and young adult patients with Crohn’s disease on both infliximab and either azathioprine or 6-mercaptopurine.\(^{29,30}\) Nevertheless, close surveillance for infections or signs of malignancy is warranted in patients on infliximab.

In our experience, given its consistent efficacy and quick onset of action, infliximab is particularly useful as rescue therapy to gain control of refractory, rapidly progressive pustular psoriasis. Though sporadic use should be limited for reasons previously mentioned, potentially life-altering or threatening situations such as severe pustular psoriasis warrants this type of use. Although undoubtedly effective, infliximab’s precise role in treating other forms of psoriasis and as maintenance therapy in children is yet to be determined.

**Adalimumab (Humira®)**

Adalimumab received FDA approval in 2008 for the treatment of JIA in patients 4 years of age and older,\(^{31,32}\) and it is currently being used off-label for pediatric inflammatory bowel disease (IBD), uveitis, and psoriasis. Adalimumab is a fully human monoclonal antibody against TNF-α and is administered subcutaneously every 2 weeks. To date, there have been no randomized controlled trials performed in the US evaluating adalimumab in pediatric psoriasis. Therefore, its use in this population remains anecdotal although results are encouraging. There are two case reports in the literature detailing the successful use of adalimumab for recalcitrant pustular psoriasis in adolescent girls after failure of other systemic and biologic agents.\(^{33,34}\)

The long-term safety of adalimumab in children with psoriasis is currently unknown. However, its safety profile in pediatric IBD and JIA is similar to that of other TNF-α inhibitors, with infections and injection site reactions being most common.\(^{2,35}\)

Given its successful use in adult psoriasis and psoriatic arthritis, convenience of every 2 week dosing, and emerging evidence of efficacy and safety in children, adalimumab is gaining popularity for individually selected cases. Outside of the US, a manufacturer-sponsored multicenter randomized double-blind study evaluating the efficacy and safety of adalimumab versus methotrexate in pediatric patients aged 4 to 17 years with chronic plaque psoriasis is underway.\(^{9}\)

**TNF Inhibitor Black Box Warning**

TNF-α inhibitors carry a black box warning for increased risk of lymphoma and other malignancies in the pediatric population. Evidence that treating children with TNF blockers may increase the risk of malignancy exists; however, reported cases were confounded by the potential risk of malignancy associated with underlying illnesses and concomitant use of other immunosuppressant agents. Thus far, a clear causal relationship between the use of TNF blockers and malignancy in children has not been established.\(^{36}\) In addition, there have been rare reports of hepatosplenic T-cell lymphoma in adolescents and young adults taking infliximab in combination with either azathioprine or 6-mercaptopurine as mentioned above.\(^{29,37}\) Although there have been no reports of malignancy in pediatric psoriasis, this potential risk must be considered and discussed with families prior to treatment initiation.

**Cytokine Inhibitor**

**Ustekinumab (Stelara®)**

Ustekinumab is a human monoclonal antibody directed against IL-12 and IL-23. This agent was recently approved for the treatment of moderate to severe plaque psoriasis in adults. It is administered via subcutaneous injection once per month for 2 months, then every 12 weeks. To date, there is one published case report detailing the use of ustekinumab in a 14 year old male with plaque psoriasis.\(^{3}\) A phase III multicenter randomized double-blind placebo-controlled trial evaluating the efficacy and safety of ustekinumab in the treatment of adolescent patients with moderate to severe plaque psoriasis (CADMUS) is underway outside of the US.\(^{38}\) Its rapid onset of action and convenient dosing schedule make it an attractive option for treatment of severe or rapidly progressive psoriasis in children; however, inadequate data exist at this time to recommend its routine use in the pediatric population.

**Case Resolution**

In the case of the 8 year old boy with rapidly progressing generalized pustular psoriasis refractory to standard first-line traditional systemic agents presented above, we opted to treat the patient with a rescue infusion of infliximab 5 mg/kg. Within 48 hours, there was a dramatic response with cessation of pustule formation, subsequent healing of existing lesions, and resolution of erythroderma. After discharge from the hospital, he failed to return to our center for his next infliximab infusion and suffered a very unstable course with multiple severe exacerbations. Because of failure of traditional first-line agents together with a complicated social situation resulting in inability to consistently attend appointments for infliximab infusions, his local dermatologist prescribed adalimumab. Ability to administer the medication at home facilitated compliance and, to date, his disease has stabilized and he has been free from exacerbation.
Conclusion

The clinical vignette highlights the central role of biologics in the management of severe presentations of psoriasis. Though not yet approved in the US for pediatric psoriasis, the anti-TNF agents are approved for other pediatric indications and for psoriasis in the EU and Brazil. At present, consideration of TNF-α inhibitors among traditional first-line agents for severe psoriasis in children is supported by the aggregate data across clinical indications. In current practice, biologics in general are often selected as second- or third-line agents for refractory cases of plaque, erythrodermic, and pustular psoriasis in children because of unknown long-term safety and challenges with insurance coverage. In the future, as experience and evidence of safety expand, specifically in the pediatric psoriasis population, biologic agents may advance to a primary position among treatment options. We look forward to having data from ongoing trials using adalimumab and ustekinumab for pediatric psoriasis to lend evidence to management decisions. In the meantime, clinical judgment is the key to appropriate use of these agents. Balancing enthusiasm regarding efficacy, tolerability, and convenience with a clinically appropriate level of caution while the long-term safety profiles of these agents are fully elucidated will assure optimal care for this unique and challenging population of patients.

References

The Health Controversies of Parabens

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ABSTRACT

Parabens are preservatives used in a variety of personal care, cosmetic, pharmaceutical and food products. Studies have confirmed the ubiquitous presence of parabens, with levels detected in wastewater, rivers, soil and house dust. Parabens have also been detected in human tissues and bodily fluids, but it is the discovery of these chemical compounds in the breast tissue of patients with breast cancer that has raised public concern over their use. It is hypothesized that the estrogenic properties of parabens may play a role in breast cancer development. However, studies investigating the health effects of parabens are conflicting. At this point, there is an insufficient amount of data suggesting serious consequences from paraben use and exposure to warrant drastic avoidance measures or government regulations.

Key words: parabens, preservatives, cosmetic products, breast cancer, spermatotoxicity, regulations, environment

Introduction

Parabens are preservatives that are used in a wide range of cosmetic, pharmaceutical and some food products. Parabens are esters of para-hydroxybenzoic acid and commonly include methylparaben, ethylparaben, propylparaben and butylparaben.1

The recent health concerns regarding parabens stem from a study published in 2004 that detected parabens in breast tissue from patients with breast cancer.2 Public pressure has persuaded several governments to introduce regulations on the use of parabens in consumer products. In this review, we examine the data regarding the health effects of parabens to provide physicians and patients with a better understanding of this issue.

Consumer Products and Parabens

Parabens have been used in food, cosmetic and pharmaceutical products since the 1930s. Their use in cosmetic consumer products is more prevalent than their utility elsewhere. Products found to contain parabens include hand soap, body lotion, shampoo, conditioner, face lotion, facial cleansers, foundation, lipstick, mascara, hair spray/mousse/gel, toothpaste and sunscreen.3,4 One study identified parabens in 44% of cosmetics tested.3 In personal care products tested in the US, concentrations of methylparaben up to 1.0% were found, with lipsticks containing the highest concentration ranging from 0.15% to 1.0%.5 The other parabens are used at concentrations lower than methylparaben in personal care products. Methylparaben and propylparaben are the most commonly used parabens in pharmaceutical products at concentrations of up to 20%;6 both of these preservatives are also used in food products such as jams, jellies, fillings and toppings at concentrations of up to 0.1%.7,8

Parabens in the Environment

Parabens have been found in urban streams into which treated or untreated effluent from wastewater treatment plants flows.6,9 Consequently, these chemical compounds have been identified in rivers and drinking water sources.6,8 Parabens have been detected in soil from agricultural fields, possibly from irrigation or fertilization practices.6,10 The dust in houses has also been found to contain parabens.11,12 Although commercially used parabens are of synthetic origin, some parabens are produced by living organisms, specifically by plants and microbes, e.g., a marine bacterial strain belonging to the genus Microbulbifer.13 Plants such as blueberries, carrots, olives, strawberries and others produce parabens (mainly methylparaben) for its presumed antimicrobial activity.14-16 Overall, the concentrations of parabens within the environment are low with water concentrations around 7 ng/L and effluent concentrations up to 6 µg/L, soil concentrations range from 0.5 to 8 ng/g while house dust contained up to 2400 ng/g.7-11

Parabens in the Human Body

Parabens can enter the human body through the skin and parenterally. The average daily total personal paraben exposure is estimated to be 76 mg, with cosmetics and personal care products accounting for 50 mg, 25 mg from pharmaceutical products, and 1 mg from food.17-19 Parabens applied to the skin are metabolized by keratinocyte carboxylesterases and the conjugated metabolites are excreted in urine and bile.20,21 Oral or intravenous parabens are metabolized by esterases within the intestine and liver.1 Parabens have been detected in urine, serum, breast milk and seminal fluid, but most worrisome has been the detection in breast tissue from patients with breast cancer.5,22-26 Some have hypothesized that the higher concentration in the upper lateral breast near the axilla correlates with exposure from underarm deodorant and an increased incidence of breast cancer development in the area.27,28 Still absolute concentrations indicate that levels of paraben within human fluids and tissue are low with average urine concentrations reported in the US ranging from 0.5 to 680 ng/mL and breast tissue concentrations ranging from 0 to 5100 ng/g of breast tissue (the median being 85.5 ng/g).25,26 These low concentrations should be interpreted in the context of known estrogenic effects of parabens, which are discussed in the next section.

Toxicity and Adverse Effects of Parabens

Human and animal studies have failed to show that parabens have any acute toxicity by various routes of administration. As such,
many of the studies examining paraben toxicity have focused on the long-term effects of chronic exposure.

The estrogenic activity of parabens was first identified in 1998 and has since been validated in vitro and in vivo.\(^1\) Parabens bind human estrogen receptors, although with affinities 10,000 to 1,000,000 times less than estradiol.\(^2\) Butylparaben and propylparaben have higher estrogenic activity than methylparaben or ethylparaben, but butylparaben and propylparaben are detected at concentrations 10 to 1000 times less than methylparaben in humans.\(^3\) The estrogenic effects in vitro have been demonstrated by uterotrophic (uterine growth) assays in mice and rats.\(^1\) However, this effect did not prevent implantation of a fertilized egg, which is considered the most sensitive measure of estrogen toxicity.\(^3\) As mentioned, it has been hypothesized that the estrogenic activity of parabens may promote breast cancer development. The concentration of estradiol in normal human breast tissue is 55.3 pg/g, suggesting there is a safety margin of 10 to 1000 times for parabens to approximate normal estradiol activity.\(^1,2\) The paraben breast cancer data shows no or low parabens in a subset of patients and there are no comparisons with normal controls.\(^2\) Hence, having not established a clear correlation, it is difficult to put forth a causal relationship between parabens and breast cancer development.

Another major area of study has been the effect of parabens on the male reproductive system, but findings are conflicting.\(^3\) One in vitro study found that human sperm were not viable when exposed to parabens at concentrations of 1 mg/mL.\(^6\) In vivo studies in mice did not replicate this result, with no spermatotoxic effects at paraben concentrations of 1%.\(^6\) Conflicting results have also been reported in rats, with one study showing decreased sperm number and activity while another study found no adverse reproductive effects.\(^5,6\) In humans, men with fertility problems including low sperm count and decreased motility were assayed for paraben exposure by measuring urine paraben levels.\(^7\) No correlation between sperm count or motility and paraben levels was found.

Parabens, as is the case for many preservatives, can be allergenic in a small subset of the population. This sensitization commonly manifests as an eczematous rash. The rates of reported sensitization to parabens range from 0.5% to 3.5%.\(^7\) These rates of sensitization are amongst the lowest of all preservatives.\(^17,18\) In addition, there are reports of immediate immunoglobulin E-mediated allergic reactions to parabens resulting in urticaria and, in one case, bronchospasm.\(^39,40\) However, these immediate allergic reactions are extremely rare.

**Government and Regulatory Control of Parabens**

Government regulatory boards have examined parabens and most have agreed that current concentrations of parabens are safe for consumer use. The European Union (EU) has set up limits on paraben use that have also been reviewed by the European Scientific Committee on Consumer Products (SCCP). In 2006, the SCCP concluded that parabens can be safely used in cosmetic products at concentrations of 0.4% for any individual paraben and 0.8% for total paraben concentrations.\(^1,4\) These limits echo the legislative limits put in place by the EU. The Danish government went further in 2011 by banning the use of parabens in personal care products intended for children younger than 3 years of age. This decision is based on the possibility of high systemic absorption from an immature metabolism and skin barrier dysfunction.\(^4\) In the United States, the Cosmetic Ingredient Review (CIR) assesses ingredients for safety and is reviewed by the US Food and Drug Administration (FDA). The CIR has recommended the same maximum paraben concentrations as suggested by the SCCP and as legislated by the EU.\(^1\) However, it should be noted that the CIR recommendations are only guidelines and manufacturers are not required to follow them. Likewise in Canada, there are no laws regulating paraben concentrations, but Health Canada agrees with the FDA and the CIR in regards to the safety of parabens and the adoption of maximum concentration guidelines.\(^4\)

**Alternatives to Parabens**

There are numerous preservatives that could be used in place of parabens. Some other commonly used preservatives include formaldehyde, quaternium-15, imidazolidinyl urea, diazolidinyl urea and dimethyldimethyl hydantoin.\(^18\) These preservatives more commonly cause allergic reactions and some pose more serious health implications, such as formaldehyde and its causal link with cancer.\(^18\) The use of “natural” preservatives has been advocated, including grapefruit seed extract (GSE).\(^48\) Unfortunately, GSE can interact with medications due to its ability to inhibit CYP3A4, an important enzyme involved in drug metabolism.\(^45\) Other natural preservatives include thymol, cinnamaldehyde, allyl isothiocyanate, citric acid, ascorbic acid and rosemary extract.\(^46,47\) These natural preservatives inhibit microbial growth in vitro, but the few studies testing antimicrobial activity in food products have provided equivocal results.\(^46,48,49\) Therefore, further studies to determine their efficacy, safety and toxicology are warranted before widespread use.

**Conclusion**

The expectation of long shelf lives and microorganism-free consumer products mandates the use of preservatives. Ideally, preservatives should be active at low concentrations against a wide variety of microorganisms without interfering with other ingredients in the product, while also remaining nontoxic to humans and available at low cost to manufacturers. Parabens have been used for over 80 years and, despite reports of adverse reactions, they have proven to be amongst the safest and most well tolerated preservatives. Although the possible association of parabens with decreased sperm quality and breast cancer does warrant continued examination, the current data does not support drastic regulations or personal restrictions to exposure. Other recently regulated chemicals, such as phthalates and bisphenol A, may serve as archetypes for continued vigilance and investigation.\(^46,51\)

**References**


Update on Drugs

<table>
<thead>
<tr>
<th>Name/Company</th>
<th>Approval Dates/Comments</th>
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<tbody>
<tr>
<td><strong>Varicella zoster immune globulin (human injection)</strong></td>
<td>The US FDA approved this varicella zoster immune globulin preparation in December 2012 for reducing the severity of varicella zoster virus (VZV) infections in high risk individuals when given within 4 days after exposure. VZV causes chickenpox in children and shingles in adults. Varizig® is made from plasma containing high levels of anti-varicella antibodies (immunoglobulin class G [IgG]) and is the only FDA approved immune globulin for VZV post-exposure prophylaxis treatment available in the US. It was designated as an orphan drug and received a priority review.</td>
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<td><strong>Lidocaine 7% + tetracaine 7% cream</strong></td>
<td>Health Canada issued a Notice of Compliance (NOC) in December 2012 to this topical local anesthetic cream indicated for use on intact skin in adults to provide local analgesia for superficial aesthetic procedures, such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal. The product uses the manufacturer’s proprietary phase-changing technology to form a pliable peel on the skin when exposed to air. A pinprick test was used to evaluate the duration of effect in 40 adults. Study findings showed the median duration of analgesia was 11 hours. With respect to the mean for time to return of sensation, there was no difference between the 30-minute and 60-minute Plagilis® application periods. However, at the end of the 13-hour study period 55% of treated subjects still reported diminished sensation. US FDA approval was granted in October 2012.</td>
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<tr>
<td><strong>Isotretinoin capsule</strong></td>
<td>Health Canada approved a New Drug Submission (NDS) in November 2012 for this novel formulation of isotretinoin indicated to treat severe, recalcitrant, nodular acne in patients 12 years of age and older. Treatment is administered orally, once or twice daily, for approximately 5 months. Compared with other currently available isotretinoin products (including Accutane®, Hoffman-La Roche Ltd.), this new formulation provides more reliable absorption under varying dietary conditions. A significant challenge for existing isotretinoin products is patient compliance, as the active ingredient must be taken with a high-fat meal to ensure consistent absorption. The rate and the extent of absorption of Epuris™ is equivalent to Accutane® under high-fat, fed conditions, however, Epuris™ is 83% more bioavailable when taken without food. Product launch in Canada is expected during the second quarter of 2013. US FDA approval was granted in May 2012 under the trade name of Absorica™.</td>
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Device News

**Laser hair therapy**

*igrow® Hair Growth Platform*

Apira Science, Inc.

The FDA granted 510(k) marketing clearance in January 2013 to this red light technology device for the treatment of androgenetic alopecia (male pattern hair loss). This system treats affected areas of the scalp, requires no manual movement, and is the first hands-free low level laser therapy hair growth device cleared by the FDA for at-home use.

**LED device for acne**

*Celluma™*

BioPhotas, Inc.

The FDA granted marketing clearance in January 2013 to this photobiopotic or light emitting diode (LED) device for six separate indications, including the treatment of acne, muscle and joint pain, muscle and joint stiffness, muscle spasm, arthritis and compromised local blood circulation.
<table>
<thead>
<tr>
<th>Type/Class of Therapy</th>
<th>Generic/Trade/Company Names</th>
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<th>Approving Regulatory Agency</th>
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<td>Acne</td>
<td>Adapalene 0.1% + benzoyl peroxide 2.5% gel Epiduo®</td>
<td>This gel formulation of adapalene and benzoyl peroxide was approved for the topical treatment of acne vulgaris in patients ≥12 years of age.</td>
<td>US FDA</td>
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<td>Galderma Laboratories</td>
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<td></td>
<td>Adapalene 0.3% gel Differin®</td>
<td>A pump dispenser for this retinoid gel formulation was approved for the topical treatment of acne vulgaris in patients ≥12 years of age.</td>
<td>US FDA</td>
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<td></td>
<td>Tazarotene 0.1% foam Fabior™</td>
<td>A new retinoid formulation was approved for the topical treatment of acne vulgaris in patients ≥12 years of age.</td>
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<td>CIP-Isotretinoin capsule Epuris™ (in Canada) Absorica™ (in US) Cipher Pharmaceuticals</td>
<td>Approval was granted to this novel formulation of isotretinoin for the treatment of severe recalcitrant nodular acne. It offers a precise, consistent, and uniform dosage delivery with an absorption characteristic that is stable with or without food when compared with traditional generic isotretinoin.</td>
<td>Health Canada / US FDA</td>
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<td>Actinic Keratosis</td>
<td>Ingenol mebutate gel (0.015%, 0.05%) Picato®</td>
<td>Ingenol mebutate gel (derived from the Euphorbia peplus plant) received approval for the topical treatment of actinic keratosis. The 0.015% formulation is used once-daily on the face and scalp for 3 consecutive days, and the 0.05% gel is used once-daily on the trunk and extremities for 2 consecutive days. The treatment course may be completed in 2-3 days.</td>
<td>US FDA</td>
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<td>Leo Pharma Inc.</td>
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<td>Imiquimod 3.75% cream Zyclara® Meda AB</td>
<td>Marketing authorization was granted to this immune response modifier for the topical treatment of actinic keratosis. Regulatory approval is valid in all European Union countries.</td>
<td>European Commission</td>
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<td>Anesthetic</td>
<td>Lidocaine 7% + tetracaine 7% cream Pliglis®</td>
<td>Approval was granted to this topical local anesthetic cream indicated for use on intact skin in adults to provide local analgesia for superficial aesthetic procedures, such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.</td>
<td>Health Canada / US FDA</td>
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<td>Nuvo Research Inc. Galderma Laboratories</td>
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<td>Brittle Nail Syndrome</td>
<td>Poly-ureaurethane 16% nail solution Nuvail™</td>
<td>This poly-ureaurethane 16% nail solution was approved for the management of fragile, damaged or brittle nails with cracking or splitting (referred to as nail dystrophy). It mechanically supports the damaged nail plate, forming a barrier that protects from further injury and strengthens the nail.</td>
<td>US FDA</td>
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<td>Innocutis Medical</td>
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<td>Dermal Fillers and Injectables</td>
<td>Hyaluronic acid-based dermal filler Belotero® Balance Merz Aesthetics/Anteis SA</td>
<td>This hyaluronic acid-based cohesive gel dermal filler was approved for the temporary correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.</td>
<td>US FDA</td>
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<td>Hyaluronic acid injectable gel Restylane-L® Medicis Aesthetics</td>
<td>Approval of an additional indication was granted to this transparent hyaluronic acid gel dermal filler to include submucosal implantation for lip augmentation in patients &gt;21 years of age.</td>
<td>US FDA</td>
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<td>Dupuytren's Contracture</td>
<td>Collagenase clostridium histolyticum Xiaflex®</td>
<td>Approval was granted to this novel, first-in-class biologic for the treatment of Dupuytren's contracture in adults with a palpable cord. The injected enzymes dissolve and weaken the contracted collagen cord. It is the only nonsurgical option for Dupuytren's disease.</td>
<td>Health Canada</td>
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<tr>
<td>Condition</td>
<td>Product Details</td>
<td>Approval Details</td>
<td>Approval Authority</td>
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<td>Hereditary Angioedema</td>
<td><strong>C1 esterase inhibitor (human)</strong>&lt;br&gt;Cinryze&lt;sup&gt;®&lt;/sup&gt;&lt;br&gt;ViroPharma Incorporated</td>
<td>This highly purified, pasteurized and nanofiltered plasma-derived C1 esterase inhibitor product was approved for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema.</td>
<td>Health Canada</td>
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<td>Herpes Zoster Virus (VZV) Infection</td>
<td><strong>Varicella zoster immune globulin (human) injection</strong>&lt;br&gt;Varizig&lt;sup&gt;®&lt;/sup&gt;&lt;br&gt;Cangene Corporation</td>
<td>This varicella zoster immune globulin preparation was approved for reducing the severity of chicken pox infections in high risk individuals when given within 4 days after exposure. It is the only FDA approved immune globulin for VZV post-exposure prophylaxis treatment available in the US.</td>
<td>US FDA</td>
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<td>Lice</td>
<td><strong>Ivermectin 0.5% lotion</strong>&lt;br&gt;Sklice&lt;sup&gt;™&lt;/sup&gt;&lt;br&gt;Sanofi Pasteur U.S.</td>
<td>Approval was granted to this broad-spectrum antiparasitic agent for the topical treatment of head lice in patients ≥6 months of age. Most infestations are eradicated with a single 10-minute application and without nit combing.</td>
<td>US FDA</td>
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<td>Melanoma</td>
<td><strong>Ipilimumab</strong>&lt;br&gt;Yervoy&lt;sup&gt;™&lt;/sup&gt;&lt;br&gt;Bristol-Myers Squibb</td>
<td>This human monoclonal antibody was approved for the treatment of metastatic melanoma. Administered intravenously, the drug blocks a T-lymphocyte antigen (CTLA-4), altering the body's ability to fight off cancerous cells and allowing the immune system to recognize, target, and attack cells in melanoma tumors.</td>
<td>Health Canada</td>
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<td><strong>Vismodegib capsule</strong>&lt;br&gt;Erivedge&lt;sup&gt;™&lt;/sup&gt;&lt;br&gt;Genentech Roche Curis, Inc.</td>
<td>Approval was granted to this hedgehog pathway inhibitor for the treatment of adults with advanced basal cell carcinoma (BCC). The drug is administered orally once-daily and is indicated for patients with locally advanced BCC who are not candidates for surgery or radiation and for patients with metastatic BCC.</td>
<td>US FDA</td>
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<td><strong>Vemurafenib tablets</strong>&lt;br&gt;Zelboraf&lt;sup&gt;™&lt;/sup&gt;&lt;br&gt;Genentech/Roche Group Plexikon/Daiichi Sankyo Group</td>
<td>Approval was granted to this oral, small molecule, kinase inhibitor for the treatment of metastatic or unresectable melanoma. Therapy is specifically indicated for patients with BRAFV600E mutation-positive melanoma. This BRAF enzyme inhibitor was approved with a companion diagnostic called the cobas® 4800 BRAF V600 Mutation Test, which determines a patient's eligibility for treatment.</td>
<td>European Commission, Health Canada</td>
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<td>Psoriasis</td>
<td><strong>Calcipotriene 0.005% + betamethasone dipropionate 0.064% topical suspension</strong>&lt;br&gt;Taclonex&lt;sup&gt;®&lt;/sup&gt;&lt;br&gt;LEO Pharma Inc.</td>
<td>This topical suspension of a vitamin D analog with a corticosteroid was approved for the treatment of body plaque psoriasis. This formulation is a first-line single therapy that is indicated for once-daily treatment of both scalp and body plaque psoriasis for up to 8 weeks.</td>
<td>US FDA</td>
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<td><strong>Calcipotriene 0.005% foam</strong>&lt;br&gt;Sorilux&lt;sup&gt;™&lt;/sup&gt;&lt;br&gt;Stiefel, a GSK Company</td>
<td>A supplemental New Drug Application (sNDA) was approved for calcipotriene foam 0.005%, expanding the sanctioned indications to include the topical treatment of plaque psoriasis of the scalp. With these recent changes, this topical synthetic vitamin D3 analog is now indicated for the treatment of plaque psoriasis of the scalp and body in patients &gt;18 years of age.</td>
<td>US FDA</td>
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<td>Psoriatic Arthritis</td>
<td><strong>Delayed-release prednisone tablets</strong>&lt;br&gt;Rayos&lt;sup&gt;®&lt;/sup&gt;&lt;br&gt;Horizon Pharma, Inc.</td>
<td>A delayed-release corticosteroid was approved as an anti-inflammatory or immunosuppressive agent to treat a wide spectrum of diseases including rheumatoid arthritis, psoriatic arthritis, polymyalgia rheumatica, ankylosing spondylitis, asthma, and chronic obstructive pulmonary disease (COPD).</td>
<td>US FDA</td>
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