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Review Article

# Novel Biological Therapies in Dermatology: Mechanisms of Action, Indications of Usage and Side Effects

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## Abstract

In recent years, research interest in biologic therapy for the treatment of various dermatologic entities has been growing. Multiple drugs have already been approved by the FDA and are rapidly becoming the mainstay in the treatment of a number of cutaneous diseases, namely psoriasis, psoriatic arthritis, melanoma, basal cell carcinoma, and many more.In this review, based on a detailed search of the literature via PubMed, we discuss novel biologic drugs recently approved by the FDA, their mechanism of action, indications, dosage, side effects and safety in pregnancy. We also present some of the newer biologics that are currently being investigated, along with promising fields of research in the treatment of numerous cutaneous diseases. The biologics discussed in part 2 of our review include Smoothened inhibitors, JAK/STAT pathway inhibitors, PI3K-AKT-mTOR pathway inhibitors, Toll-like receptor 9 agonists, and other tyrosine kinase inhibitors. Part 1 discusses interleukin inhibitors and BRAF and MEK inhibitor combinations.

**Keywords:** BRAF; Interleukin inhibitors; JAK/STAT; MEK; Psoriasis

## Introduction

In recent years, research interest in biologic therapy for the treatment of various dermatologic entities has been growing. Multiple drugs have already been FDA approved and are rapidly becoming the mainstay in the treatment of these cutaneous diseases, namely psoriasis, psoriatic arthritis, melanoma, basal cell carcinoma, and many more. The FDA defines biologics as medical products made from natural sources, whether human, animal or microorganism, that are intended to treat diseases and medical conditions. This review explores novel biologic drugs recently approved by the FDA, their mechanism of action, indications, dosage, side effects and safety in pregnancy. It also presents some of the newer biologics that are currently being investigated, along with promising fields of research in the treatment of numerous cutaneous diseases.

## Methods

A detailed, comprehensive search of the literature was accomplished via PubMed searches of biologic therapies used in dermatologic diseases. Reviews, case reports, case series, clinical trials, randomized controlled trials, prospective and retrospective studies were analyzed and inspected.

- **Smoothened inhibitors (Figure 1)**

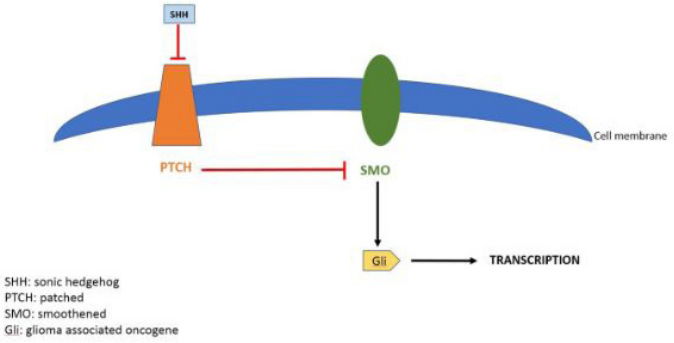


**Figure 1:** Continuous activation of SHH inhibits PTCH and subsequently continuous activation of SMO and downstream Gli resulting in basal cell carcinomas. SMO inhibitors will deactivate the continuous activation of the pathway and reduce the development of BCCs.

To date, two hedgehog pathway inhibitors (both smoothened inhibitors) have been approved by the FDA: vismodegib and sonidegib.

## Sonidegib

### Year of introduction

The use of sonidegib (ODOMZO; Novartis) for the treatment of patients with locally advanced basal cell carcinoma not amenable to curative surgery or radiotherapy was approved by the FDA in July 2015 [1].

### Mechanism of action

Sonidegib belongs to a class of biphenyl carboxamides with a novel structure [2]. and functions as an oral hedgehog pathway inhibitor (smoothened inhibitor) [3]. It interacts with the drug-binding pocket of smoothened (SMO), which mainly consists of three amino acids: arginine (R) 473, arginine (R) 400, and glutamic acid (E) 518. There, it acts as an antagonist, preventing downstream activation of hedgehog pathway signaling[2].

### Formulation

200 mg oral pill [2], taken daily on an empty stomach, at least 1 hour before or 2 hours after a meal [4].

### Uses/indications

### Basal cell carcinoma

Locally advanced BCCs, which represent 1% of BCCs, encompass tumors in facial sites that are difficult-to-treat, aggressively recurrent tumors, large neglected tumors, and those in which current treatment options are not feasible [1].

The BOLT study was a phase II, multicenter, randomized, double-blinded clinical trial in which BCC patients took either 200 or 800 mg sonidegib daily. Over 50% of patients in the 200-mg study arm reported objective responses, whereas the response in the 800 mg study arm was lower. Long-term follow-up of patients in this study showed that 200 mg sonidegib has a better treatment profile over 800 mg, and it maintains extended efficacy [2]. Although sonidegib has been shown to be effective in the treatment of advanced BCC, its use in patients previously treated with vismodegib is not effective, as the majority of these patients develop resistance [5].

### Side effects/contraindications/warnings

No major common side effects are reported. The most common adverse events occurring in ≥10% of patients were muscle spasms, alopecia, dysgeusia, decreased appetite, nausea, fatigue, myalgia, increased serum creatine kinase, and vomiting decreased weight, and diarrhea [1,2].

### Use in pregnancy, breastfeeding, and spermatogenesis

Hedgehog pathway inhibitors are contraindicated in women who are either pregnant or breastfeeding. Because hedgehog signaling plays a pivotal role in embryonic development, inhibitors of this pathway may result in death or severe birth defects in the developing fetus. Currently there are no data available regarding their levels in human milk; however, breastfeeding is not advisable during treatment and for at least 20 months after the last dose of sonidegib [4].

## DenileukinDiftitox

## Year of introduction

Denileukindiftitox (Ontak) was approved by the FDA in 1998 for the treatment of cutaneous manifestations of relapsed CTCL at dose levels of 9 or 18 μg/kg [6].

## Mechanism of action

Denileukindiftitox (DD) is a fusion protein chemotherapeutic agent that binds selectively to the high- and intermediate-affinity interleukin-2 receptor (CD25+) on lymphocytes. Once internalized by these cells, the diphtheria toxin portion of fusion protein is cleaved by proteolytic enzymes, causing cell death [7].

### Formulation

Injectable solution [6].

### Uses/indications

Cutaneous T Cell Lymphoma

Good candidates for denileukindiftitox include CTCL patients who fail interferon and oral bexarotene or those who have tumors or nodal disease (stage IIB to IV MF) [6]. An open-label phase III trial, evaluated the safety and efficacy of denileukindiftitox (18 μg/kg/day intravenously on days 1-5 of a 21-day cycle, for ≤8 cycles) in twenty patients with cutaneous T-cell lymphoma

(CTCL) who relapsed after responding to denileukindiftitox primary treatment in an earlier placebo-controlled trial. The overall response rate was 40%, mostly partial responses; nine patients experienced progression [8].

**Side effects/contraindications/warnings**

Denileukindiftitox does not cause myelosuppression. The most common frequent and clinically significant adverse events associated with its use, which physicians should look out for include: nausea, upper respiratory tract infections, fatigue, pyrexia, hypersensitivity rash, rigors, and capillary leak syndrome[7-9]. Other side effects include hypersensitivity rash, hepatobiliary disorders, transient elevation of hepatic transaminases, and visual changes, and thyroiditis with subsequent hypothyroidism. Many DD-associated adverse effects can be successfully managed with prudent use of supportive measures, without dose reduction or interruption of treatment [7].

**Follow-up and screening**

Complete blood count, liver function tests, albumin [7].

**Use in pregnancy, breastfeeding, and spermatogenesis**

N/A

**Tofacitinib (Figure 2)**

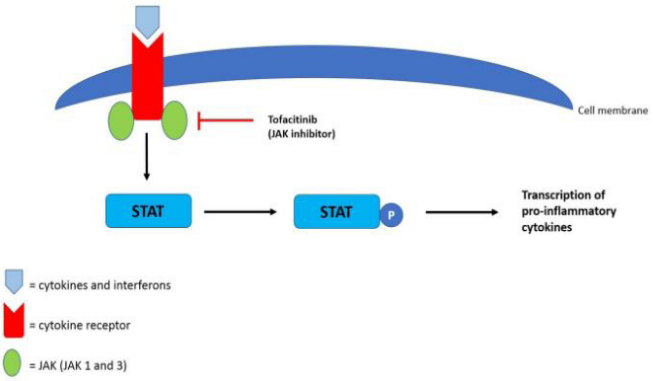


**Figure 2:** Tofacitinib will bind to the JAK attached to a cell surface cytokine receptor and subsequently block the JAK-STAT pathway thus reducing the inflammatory process.

**Year of introduction**

**Formulation**

Tofacitinib (Xeljanz and Jakvinus) is an orally available compound and the first member of the JAK inhibitors, a novel class of medication [10].

**Mechanism of action**

It inhibits phosphorylation of JAK1 and JAK3, IL-6-driven phosphorylation of STAT1 and STAT3, and STAT5 [11,12]. It functions as a pan-JAK inhibitor, preferentially inhibiting JAK1 and JAK3 and, to a lesser extent, JAK2. Its primary targets are dendritic cells, Th1 and Th17 CD4(+) T-cells, and activated B-cells involved in multicytokine targeting [13]. It inhibits antigen presentation and T-cell stimulation by dendritic cells, inhibits differentiation and antibody production of B cells, and limits the production of IL-17A, IL-17F, and IL-22, the expression of the IL-23R, and the differentiation of Th1 cells [13].

**Uses/indications**

**Alopecia areata**

A two-center, open-label, single-arm trial assessed the effects of using twice daily dosing of 5mg tofacitinib in 66 patients with alopecia areata, totalis, and universalis for three months. Tofacitinib was found to be a safe and effective treatment for severe alopecia areata, though it does not result in a durable response once treatment is withheld, with disease relapse after an average of 8.5 weeks [14].

**Psoriasis**

Chronic plaque psoriasis is the most common form of the disease that is clinically characterized by well-delineated red and scaly plaques. Recently, oral and topical formulations of tofacitinib have been demonstrated to be safe and effective for the treatment of plaque psoriasis in randomized clinical trials. In particular, a 10-mg bid dose of tofacitinib was shown to be noninferior to etanercept 50 mg subcutaneously twice weekly.

A phase 3, randomised, multicentre, double-dummy, placebo-controlled, 12-week, non-inferiority trial, showed that treatment of adult patients with moderate to severe chronic stable plaque psoriasis, with 10 mg twice daily dose of tofacitinib was non-inferior to etanercept 50 mg twice weekly and was superior to placebo (whereas the 5 mg twice daily dose did not show non-inferiority to etanercept 50 mg twice weekly). Furthermore, the adverse event rates over 12 weeks were similar for tofacitinib and etanercept [15]. The results of two randomized studies that investigated the safety and efficacy of a topical solution of tofacitinib in patients with chronic plaque psoriasis were unrevealing [16,17].

**Atopic Dermatitis**

Tofacitinib citrate given to six consecutive patients with moderate-to-severe atopic dermatitis showed a decrease in body surface area involvement of dermatitis and decreased erythema, edema/papulation, lichenification, and excoriation, with no adverse events [18].

**Side effects/contraindications/warnings**

As with other immunomodulatory drugs, the risk of tuberculosis and other opportunistic infections may potentially be elevated in patients treated with tofacitinib. Other side effects include a de-

crease in hemoglobin, neutrophil, and lymphocyte counts, as well as an increase in creatinine, alanine aminotransferase, and lipid levels (total cholesterol, HDL, and LDL). Most of these abnormalities are transient and reversible either spontaneously or with discontinuation of the drug [19, 20] and resemble the safety profile of etanercept [15].

70% of the total clearance of tofacitinib involves nonrenal elimination. It is metabolized primarily by cytochrome P450 3A4 (CYP3A4), therefore interacting with potent inhibitors (ex. ketoconazole) or inducers (ex. rifampin) of CYP3A4 and inducers or inhibitors (ex. fluconazole) of CYP2C19 [10].

**Use in pregnancy, breastfeeding, and spermatogenesis**

Pregnancy category: C

Lactation: unknown whether distributed in human breast milk [10].

- PI3K-AKT-mTOR pathway inhibitors (Figure 3)

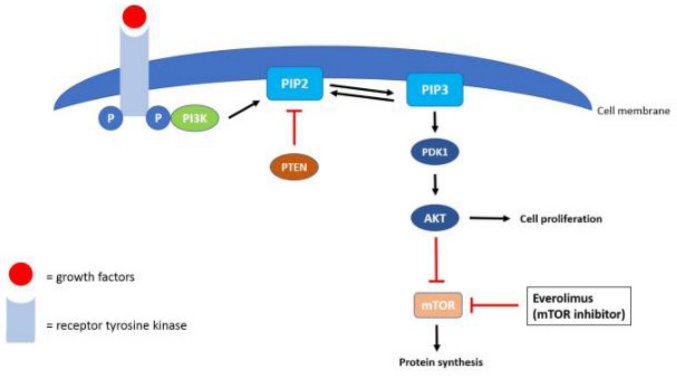


**Figure 3:** Showing the PI3K-AKT-mTOR pathway which is involved in cellular proliferation and protein synthesis. Everolimus will inhibit the action of mTOR.

## Everolimus

### Year of introduction

Everolimus (Afinitor) was FDA approved in 2010 for the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) in patients who are not suitable for surgical intervention [21].

## Mechanism of action

Everolimus is a derivative of sirolimus, and works by inhibiting mTOR (mammalian target of Rapamycin). It binds to the FK binding protein-12, forming a complex which inhibits the activation of mTOR, leading to a reduction of cell proliferation and protein synthesis. It also inhibits the expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor, leading to a reduction in angiogenesis [22].

### Formulation

Everolimus is found in the form of tablets, or tablets for oral suspension. It is available in 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets [23].

### Uses/indications

### Relapsed T-cell lymphoma

A phase II trial was conducted in which patients with relapsed T-cell lymphoma were treated with the single-agent mTORC1 inhibitor everolimus, at the FDA-approved dose of 10mg/day. 7 out of 16 patients enrolled in this trail had Mycoses Fungoides (stage IIB or stage II). 43% of these patients attained a partial response to everolimus [22, 24].

### Morphea

A case report published in 2016 indicates that Mtor inhibition is a promising treatment for severe morphea.

A 57-year-old female, with severe morphea, was started on 0.5 mg twice daily of everolimus after failure of multiple lines of treatment. This treatment showed significant clinical improvement in 6 months, with a Rodnan score reduction of 43 to 22 of 51. Further studies are needed [25].

### Uveal melanoma

A recent study pulished in 2014 identified a strong synergy between the mTOR inhibitor Everolimus and the PI3K inhibitor GDC0941. When given in combination to treat uveal melanoma, they found increase in apoptosis of the malignant cells compared to monotherapies, with increased anti-tumor effect [26]. Another phase 2 trial enrolling 14 patients with progressive metastatic uveal melanoma administered 10mg daily of everolimus with a long acting somatostatin analog. This combination stabilized their disease for about 16 weeks, however it was associated with a high rate of adverse events [27].

### Metastatic melanoma

Multiple phase II trials considered the combination of everolimus and paclitaxel and carboplatin therapy for the treatment of metastatic melanoma. However, these trials failed to show any superiority, and these therapies were not recommended [28].

### Side effects/contraindications/warnings

Physicians should warn their patients about the most common adverse reactions that were associated with Everolimus. These include stomatitis, infections, rash, fatigue, diarrhea, edema, fever, abdominal pain, headache and decreased appetite. Everolimus interacts with multiple drugs including CYP3A4 inhibitors (e.g.,Cyclosporine, Ketoconazole, Erythromycin, Verapamil) and CYP3A4 inducers (e.g., rifampin). Prescribing Everolimus is contraindicated in patients with hypersensitivity to the drug [23].

**Follow-up and screening**

When a patient is started on everolimus, the treating physician should order baseline as well as periodic lab studies are required to follow up. These studies include: CBC, BUN, creatinine, urinary protein, liver function tests and a metabolic panel.

**Use in pregnancy, breastfeeding, and spermatogenesis**

Pregnancy Category D: There are no adequate and well controlled studies of everolimus in pregnant women. Hence, women of childbearing age should use highly effective contraceptive methods while and up to 8 weeks after receiving everolimus. As for nursing mothers, it is better to avoid taking everolimus while they are breastfeeding and for 2 weeks after the last dose, as it is unknown whether everolimus is excreted in human breast milk [23].

## Cabozantinib

**Year of introduction**

Cabozantinib (Cometriq, Cabometyx) FDA approved in April 2016 for the treatment of advanced renal cell carcinoma [23].

**Mechanism of action**

Cabozantinib is a tyrosine kinase inhibitor with multiple targets including VEGF receptor, PDGF receptor, and c-kit. It inhibits metastasis, angiogenesis, and tumor growth [29].

**Formulation**

Oral tablets or capsules.

**Uses/indications**

**Metastatic melanoma**

A phase II randomized discontinuation trial evaluated the role of cabozantinib in the treament of metastatic melanoma. All patients included in the trail received cabozantinib 100mg daily for 12 weeks.Then, patients who had stable disease at week 12 were randomized to receive either cabozantinib or placebo. This study concluded that Cabozantinib has clinical activity in patients with metastatic melanoma, including uveal melanoma. Further clinical investigation is warranted [30].

**Side effects/contraindications/warnings**

Cabozantinib use is associated with many side effects that the primary physician should look out for including hypertension, fatigue, voice disorder, headache, palmar-plantar erythrodysesthesia, hair discoloration, rash, diarrhea, stomatitis, lumphocytopenia etc [31, 32].

**Use in pregnancy, breastfeeding, and spermatogenesis**

It is contraindicated in pregnant or lactating women.

## Toll-like receptor 9 agonist (TLR9)

**Mechanism of action**

TLR9 agonists directly induce activation and maturation of plasmacytoid dendritic cells and enhance differentiation of B cells into antibody-secreting plasma cells. TLR9 detects ssDNA molecules that contain unmethylated CpG-containing motifs commonly found in viral genomes, enhancing the development of antitumor T-cell responses [33].

TLR9 agonists are currently being studied in combination with ipilimumab, a recombinant human monoclonal antibody and in patients with unresectable or metastatic melanoma [34].

**Uses/indications**

**Melanoma and basal cell carcinoma**

A phase 1 study was conducted by Hoffman et al. on PF-3512676, a TLR9 agonist. Patients with BCC and melanoma were given intra lesional injections of escalating doses of PF-3512676. 4 out of 5 patients with BCC had partial regression of the lesion, and 1 patient had complete regression. 1 out of 5 patients with metastatic melanoma had complete regression of the lesion [35].

**Mycosis fungoides**

A single institution phase 1/2 study evaluating the safety, feasibility, and efficacy of in situ vaccination using intratumoral CpG injections combined with local low-dose radiation was conducted on 15 patients with MF who had failed standard therapy. 5 out of 15 patients had clinically meaningful responses, with only mild tolerable side effects [36].

**Side effects/contraindications/warnings**

TLR9 agonists are generally well tolerated. The most common adverse effects include flu-like symptoms and local injection site reactions such as inflammation, pain, edema and erythema [37].

**Crizotinib**

Year of introduction

Crizotinib (Xalkori) was FDA approved in March 2016 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) and in 2011 for the treatment of patients anaplastic lymphoma kinase (ALK)-positive tumors [38].

**Mechanism of action**

Crizotinib selectively inhibits the ALK tyrosine kinase, reducing keratinocyte proliferation and decreasing the expression of GLI1 and CCND2 MRNA (members of the sonic hedgehog pathway). The SHH pathway was also found to be associated with the development of basal cell carcinoma (BCC).

**Formulation**

Available in the form of capsule, given 250 mg twice daily [39].

**Uses/indications**

**Basal cell carcinoma**

Ning et al. demonstrated by laser capture micro dissection in combination with CDNA microarray analysis that ALK is over expressed and phosphorylated in BCC tissue, thereby implicating ALK as a potential target in the treatment of BCC [40].

**Side effects/contraindications/warnings**

The primary physician should expect the following side effects: edema, bradycardia, fatigue, vision disturbances, nausea vomiting, diarrhea or constipation. Crizotinib should be avoided in patients with long QT syndrome, and the physician should discontinue the drug in case a patient develops long QT syndrome. Amino transferases and bilirubin levels should be monitored regularly [39].

**Use in pregnancy, breastfeeding, and spermatogenesis**

Pregnancy category D drug

It is not known if crizotinib is excreted in breast milk.

## Conclusion

Our review (parts 1 & 2) is not all-inclusive. Ongoing research is - and will keep - revealing new indications for existing biologics as well as new biologic agents. We have described a few biologic therapies that have recently been used as dermatologic treatments. With the promising fields of research in the treatment of numerous cutaneous diseases, we look forward to the exploration of new agents and indications.

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