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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 1 of our review include interleukin inhibitors and BRAF and MEK inhibitor combinations. Part 2 discusses Smoothened inhibitors, JAK/STAT pathway inhibitors, PI3K-AKT-mTOR pathway inhibitors, Toll-like receptor 9 agonists, and other tyrosine kinase inhibitors.

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.

Ustekinumab

Year of introduction

Ustekinumab (Stelara) was approved by the FDA in 2009 for the treatment of moderate to severe plaque psoriasis. It was also approved in 2013 for the treatment of adult patients with active psoriatic arthritis, alone or in combination with methotrexate [1].

Mechanism of action

A fully human monoclonal antibody of the IgG1 class di-

rected against the shared p40 subunit of cytokines IL-12 and IL-23, inhibiting their pro-inflammatory effect [1].

Formulation

Injectable solution for intravenous or subcutaneous administration [1].

Uses/indications

Plaque Psoriasis and Psoriatic arthritis

Multiple studies have assessed the use of ustekinumab in the treatment of psoriasis and psoriatic arthritis; indeed, this drug received FDA approval for the treatment of psoriasis in 2009 and psoriatic arthritis in 2013 [1].

Acrodermatitis continua of Hallopeau (ACH)

ACH is a variant of pustular psoriasis that is often very difficult to treat. Almost all anti-psoriatic agents have been used in the treatment of ACH. Adisen et al. present the case of a 50-year-old male with ACH resistant to anti-tumor necrosis factor-α agents. Initial therapy with ustekinumab achieved a sustained response; however, after seven months of interruption, retreatment resulted in a slower and poorer response than the initial regimen.

Palmoplantar Pustular Psoriasis

Buder et al demonstrated evidence for the effectiveness and tolerability of ustekinumab in the treatment of palmoplantar postural psoriasis in a case series of nine patients who were treated with ustekinumab, with resultant improvement in symptoms and minimal side effects (local injection site reactions and mild infections). However, long-term efficacy, safety, and therapeutic benefit are yet to be validated [2].

Side effects/contraindications/warnings

The most common reported side effect is upper respiratory tract infection, which primary care physicians must warn patients about and be on the lookout for. Other less common side effects include nasopharyngitis, back pain, cellulitis, depression, diarrhea, fatigue, headache, myalgias, and antibody formation [1].

Use in pregnancy, breastfeeding, and spermatogenesis

Pregnancy Category: B

Lactation: use caution [1].

- IL-17 inhibitors (Figure 1)

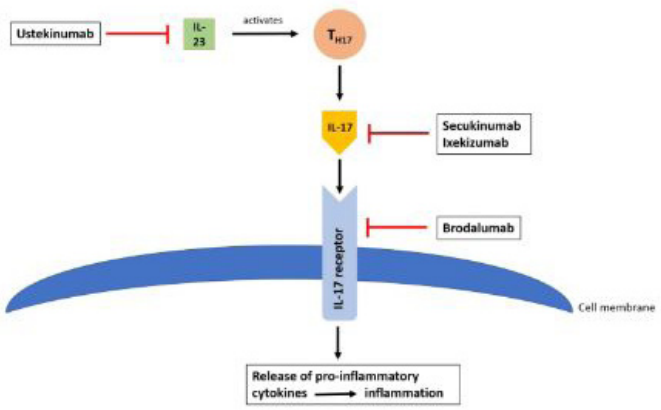

Figure 1: Showing the site of action of the four different drugs that inhibit the IL-17 signaling pathway.

Brodalumab

Year of introduction

Brodalumab (Siliq) was FDA approved in February 2017 for the treatment of moderate-to-severe plaque type psoriasis [3].

Mechanism of action

Brodalumab is a human IgG2 monoclonal antibody that binds with high affinity to IL-17 Receptor A and inhibits its activity by decreasing its downstream effect and the release of pro-inflammatory cytokines and chemokines [4].

Formulation

Injections administered subcutaneously.

Uses/indications

It was FDA approved for the treatment of moderate to severe plaque-type psoriasis, psoriatic arthritis, pustular psoriasis and psoriatic erythrodermain adult patients who are candidates for systemic therapy/phototherapy and have failed to respond to other systemic therapies [5].

The recommended dosage is 210 mg in 1.5 ml solution subcutaneously at weeks 0, 1 and 2, and then every 2 weeks [6].

Moderate-to-severe plaque psoriasis

The AMAGINE-1 trial, a phase-3, double-blind, placebo-controlled, randomized trial, showed that PASI75 was achieved in 83.3% of patients treated with 210 mg of Brodalumab, and in

60.3% of patients treated with 140 mg versus placebo. Clinical improvements were maintained through weak 52. PASI100 was also noted in 23.3% of patients in the 140-mg group and 41.9% of the 210 mg group [7].

Furthermore, the AMAGINE-2 and AMAGINE-3 trials evaluated the efficacy and safety of Brodalumab compared to placebo. These trials showed that 86% of patients treated with Brodalumab achieved PASI75 after 12 weeks compared to 8.1% of patients treated with placebo [8].

Generalized pustular psoriasis (GPP) and psoriatic erythroderma (PsE)

An open-label, multicenter, long-term phase III study in assessed the efficacy of brodalumab 140 mg at day 1 and weeks 1 and 2, and then every 2 weeks until week 52 Japanese patients with GPP and PsE. Brodalumab significantly improved the symptoms of patients with GPP and PsE throughout the 52 weeks, and demonstrated favorable safety profiles [9].

Psoriatic arthritis

A phase II RCT was conducted in 2014 comparing brodalumab (140 mg or 280 mg) vs. placebo in the treatment of psoriatic arthritis was stopped in May 2015 due to potentially increased risk of depression and suicidal ideation associated with Brodalumab [10].

Side effects/contraindications/warnings

The most frequently reported adverse events that treating physicians should look out for include nasopharyngitis, upper respiratory tract infection, headache and mild, treatable cases of candidiasis and Tinea infection [7]. As with most immune modulatory drugs, patients are at an increased risk for opportunistic infections, including reactivation of latent tuberculosis. If serious infections occur, the drug should be immediately discontinued. Patients should also be evaluated for TB infection prior to initiating treatment with Brodalumab.

Brodalumab is contraindicated in patients with Crohn's disease. Over expression of IL-17 is implicated in the pathogenesis of Crohn's disease [11]. A randomized, double blind, placebo-controlled study conducted to evaluate the safety, tolerability, and efficacy of was terminated early due to worsening of Crohn's disease in patients in the treatment arm compared to the control [11, 12]. Brodalumab has also been associated with an increased risk of suicide behavior but this was no significant according to Chiricozzi et al. [12].

Use in pregnancy, breastfeeding, and spermatogenesis

Human IgG are known to cross the placenta, however there are no human studies to determine whether Brodalumab is transmitted from mother to fetus or whether it is distributed in breast milk.

Ixekizumab

Year of introduction

Ixekizumab (Taltz) was FDA approved in March 2016 for the treatment of moderate-to-severe plaque psoriasis [13].

Mechanism of action

Humanized IgG4 monoclonal antibody that selectively binds IL-17A and inhibits the release of pro inflammatory cytokines and chemokines [14].

Formulation

Injections, administered subcutaneously.

Uses/indications

The recommended dose of Ixekizumab is 160 mg given subcutaneously once, followed by 80 mg at weeks 2, 4, 6, 8, 10 and 12, and then 80 mg every 4 weeks [15].

Moderate to severe psoriasis

UNCOVER-2 and UNCOVER-3 are prospective, double-blind, multicenter, phase-3 studies in which patients with moderate to severe plaque type psoriasis received subcutaneous placebo, etanercept (50 mg twice weekly) or ixekizumab 160 mg starting dose followed by 80 mg every 2 weeks or every 4 weeks. This study demonstrated that 90% of patients receiving ixekizumab every 2 weeks achieved PASI75 at week 12 with rapid onset of efficacy. A higher percentage of patients receiving Ixekinumab every 2 weeks achieved PASI90 at 12 weeks compared to every 4 weeks (71% vs. 60% in UNCOVER-2, and 68% vs. 65% in UNCOVER-3). In comparison, only 19% (UNCOVER-2) and 26% (UNCOVER-3) of patients achieved PASI90 at 12 weeks with etanercept therapy [14].

Psoriatic arthritis

SPIRIT-P2 is randomized, double-blind, placebo-controlled phase 3 trial in which patients with psoriatic arthritis who have had inadequate response to TNF-inhibitors were randomly assigned to receive ixekizumab every 4 weeks, ixekizumab every 2 weeks, or placebo. ACR-20 was achieved in 53% of patients in the ixekizumab every 4 weeks group, compared to 40% of patients in the ixekizumab every 4 weeks group and 20% of placebo patients [16].

Side effects/contraindications/warnings

Refer to Bordalumab side effects above.

Use in pregnancy, breastfeeding, and spermatogenesis

Similar to Brodalumab.

Secukinumab

Year of introduction

Secukinumab (Cosentyx) was FDA approved in January 2015 for the treatment of plaque psoriasis. It was later approved in January 2016 for the treatment of patients with ankylosing spondylitis and psoriatic arthritis [17, 18].

Mechanism of action

Secukinumab is a monoclonal antibody that selectively binds to and inhibits the pro-inflammatory cytokine interleukin IL-17A [17].

Formulation

Lyophilized powder or solution for subcutaneous injection [17].

Uses/indications

soriasis and Psoriatic Arthritis

Recent studies have highlighted the importance of T helper 17 cells and associated pathologic enhanced expression of the cytokine interleukin-17A (IL-17A). As integral players in the pathogenesis of psoriasis and psoriatic arthritis. Novel biologic therapies targeting the IL-17 pathway have been found to be highly effective.

In treating patients with moderate-to severe plaque psoriasis and psoriatic arthritis in clinical trials [19]. Of those, only secukinumab has received Health Canada and US Food and Drug Administration approval for treatment of moderate-to-severe psoriasis, as well as the US Food and Drug Administration approval for treatment of psoriatic arthritis and ankylosing spondylitis (but not pustular psoriasis).

In head-to-head studies, secukinumab has been found to be more effective than etanercept and ustekinumab, particularly in achieving Psoriasis Area and Severity Index (PASI) 90/100 and achieving PASI 50/75 as early as week 4 [20].

In summary, secukinumab is an effective and safe treatment option that attains high clearance rates up to PASI 90 and 100 as monotherapy in cases of moderate-to-severe psoriasis. It may be particularly helpful in patients with psoriasis who have formed antidrug antibodies or failed other biologic agents and in patients with psoriatic arthritis or ankylosing spondylitis [20].

Pityriasis Rubra Pilaris (PRP)

The use of secukinumab has been reported in a 33-year-old female with a 9-year history of PRP, who had failed or relapsed after multiple therapeutic modalities including topical corticosteroids, acitretin, photo chemotherapy, immune modulators, and biologics. After treatment with 5 subcutaneous 300-mg weekly injections of secukinumab, followed by once a month injection, in association with cyclosporine and 10mg of prednisone, a significant and prompt clinical response and quality-of-life improvement were observed [21].

Side effects/contraindications/warnings

Physicians should inform their patients that 10-30% of patients may report infections and nasopharyngitis. Less common side effects include diarrhea, upper respiratory tract infection, rhinitis, oral herpes, rhinorrhea, and urticaria [17].

According to Malakouti et al. safety data for secukinumab is comparable to available biologics.

Use in pregnancy, breastfeeding, and spermatogenesis

Pregnancy category: B.

Lactation: unknown [17].

- BRAF and MEK inhibitor combinations (Figure 2)

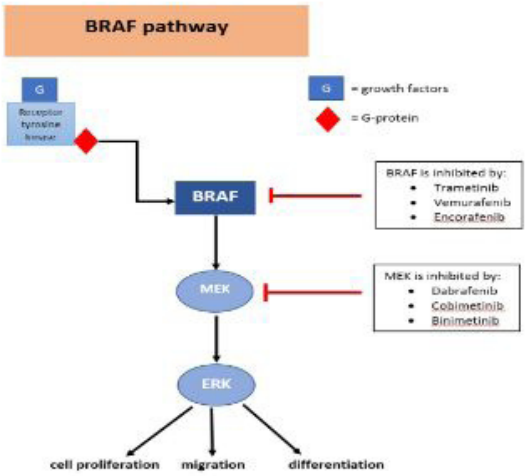

Figure 2: Showing the site of action of the six different medications in inhibiting the BRAF pathway whether at the level of the BRAF itself or downstream at the level of MEK.

The Ras-regulated RAF/MEK/ERK pathway is involved in the pathogenesis of melanoma. This pathway regulates cell proliferation, migration, differentiation, angiogenesis etc. In tumors that are BRAF mutation positive. Administering selective BRAF or MEK inhibitors was associated with increased overall survival in melanoma patients [22].

Trametinib and dabrafenib

Year of introduction

Trametinib (Mekinist) was FDA approved in 2013 for treatment of unresectable or metastatic melanoma with a positive BRAF V600E/K mutation. FDA approved in 2014 in combination with dabrafenib (Tafinlar), a BRAF inhibitor [23].

Mechanism of action

Trametinib: selective inhibitor of MEK1/1

Dabrafenib: BRAF inhibitor

Formulation

Both are available in oral formulation given at dose of 2 mg daily (Trametinib) and 150 mg twice daily (Dabrafenib) [24].

Uses/indications

Metastatic/unresectable melanoma

The METRIC study is a Phase III, randomized, open-label, multisite study in which patients with advanced or metastatic BRAF V600E/K mutation-positive melanoma were randomized to receive trametinib vs. chemotherapy (dacarbazine or paclitaxel). After 6 months, trametinib demonstrated a significantly higher overall survival compared to chemotherapy (81% vs. 67%, P=0.01) [22].

Trametinib in combination with dabrafenib showed significant benefit in the treatment of melanoma as compared to Trametinib monotherapy. A multicentre, double-blind, phase 3 randomized controlled trial comparing the combination vs. monotherapy and placebo concluded that overall survival was significantly higher in the combination group compared to the dabrafenib group at 1 year (74% vs. 68% respectively) and at 2 years (51% vs. 42%) with a higher median progression-free survival (11 vs. 8.8 months) [25].

Side effects/contraindications/warnings

Adverse events were generally similar in trametinib monotherapy and combination of trametinib and dabrafenib. Physicians should inform their patients that they might experience rash, diarrhea, gastrointestinal disturbances and edema [24]. However, the trametinib-dabrafenib combination was associated with significantly higher rates of pyrexia, hyperkeratosis, arthralgia [25] and major hemorrhagic events and venous thrombo embolism.

Follow-up and screening

Treating physicians should perform a baseline CBC and liver function testing on their patients with periodic follow up along with an echocardiogram, repeated 1 month after therapy initiation, and then at 2- to 3-month intervals as the drugs were associated with cardio myopathy [24].

Use in pregnancy, breastfeeding, and spermatogenesis

Pregnancy category D.

It is unknown whether these drugs are also excreted in breastmilk.

Vemurafenib and cobimetinib

Year of introduction

Vemurafenib (Zelboraf) was FDA approved in August 2011 for the treatment of late stage/unresectable melanoma [26]. FDA approved in combination with Cobimetinib (Cotellic) in November 2015 [27].

Mechanism of action

Vemurafenib: selective inhibitor of mutant BRAF V600E

Cobimetinib: MEK inhibitor.

Formulation

Both are available in oral formulation given at dose of 960 mg every 12 hours (Vemurafenib)and 60 mg daily (Cobimetinib) for 21 out of 28 days of the treatment cycle [28].

Uses/indications

Metastatic or Unresectable melanoma

Larkin et al. conducted a randomized phase 3 study in which 495 patients with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation positive melanoma were randomly assigned to receive combination therapy with vemurafenib+cobimetinib, or vemurafenib+placebo.

The group receiving combination therapy showed a significant increase in progression-free survival compared to the control group (9.9 vs. 6.2 months) and a higher rate of complete or partial response (68% vs. 45%). The combination was however associated with increased toxicity [29].

Side effects/contraindications/warnings

Vemurafenib was associated with the development of new primary cutaneous malignancies and new non-cutaneous squamous cell carcinomas. A frequent dermatologic evaluation is recommended for up to 6 months following discontinuation of the drug. The combination was associated with lower rates of squamous cell carcinoma compared to monotherapy (2% vs. 11%) [29]. Physicians should also inform their patients of other side effects including arthralgia, fatigue, rash, photosensitivity, hepatotoxicity, severe hypersensitivity reactions including DRESS syndrome [28].

Follow-up and screening

Similar to trametinib and dabrafenib.

Use in pregnancy, breastfeeding, and spermatogenesis

Vemurafenib and cobimetinib can cause fetal harm. Placental transfer of vemurafenib to the fetus has been reported.

Encorafenib and Binimetinib

Year of introduction

This combination is currently being studied in trials for the treatment of melanoma

Mechanism of action

Encorafenib: BRAF inhibitor

Binimetinib: MEK inhibitor.

Formulation

Binimetinib is given at a dose 45 mg orally twice daily. Encorafenib is currently being tested at different oral doses (400, 450, or 600 mg once daily) in various studies [30].

Uses/indications

BRAF-mutant melanoma

The combination of encorafenib and binimetinib is currently being studied in a phase 3 trial for the treatment of BRAF mutant melanoma. The COLOMBUS trial is an ongoing randomized, open label, multi-center, parallel group, phase III study comparing the combination of encorafenib and binimetinib to vermurafenib and to encorafenib monotherapy in patients with locally advanced, Unresectable or metastatic BRAF V600 mutation positive patients. It demonstrated that the combination of encorafenib and binimetinib significantly improved progression free survival compared to vemurafenib and encorafenib monotherapy (14.9 vs. 7.3 vs. 9.6 months respectively) [30].

Side effects/contraindications/warnings

The safety profile was more favorable in patients receiving the combination therapy compared to vemurafenib or encorafenib monotherapy. The most common side effects that physicians should expect include elevations in transaminases, nausea, vomiting, pyrexia and increased creatinine phosphokinase [30].

Use in pregnancy, breastfeeding, and spermatogenesis

Precautions to avoid during pregnancy and breast feeding.

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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