Expert Opinion on Therapeutic Patents

ISSN: 1354-3776 (Print) 1744-7674 (Online) Journal homepage: http://www.tandfonline.com/loi/ietp20

Small molecules and antibodies for the treatment of psoriasis: a patent review (2010-2015)

Andrea Chiricozzi, Rosita Saraceno, Lucia Novelli, Monika Fida, Francesco Caso, Raffaele Scarpa, Luisa Costa, Roberto Perricone, Marco Romanelli, Sergio Chimenti & Maria Sole Chimenti

To cite this article: Andrea Chiricozzi, Rosita Saraceno, Lucia Novelli, Monika Fida, Francesco Caso, Raffaele Scarpa, Luisa Costa, Roberto Perricone, Marco Romanelli, Sergio Chimenti & Maria Sole Chimenti (2016): Small molecules and antibodies for the treatment of psoriasis: a patent review (2010-2015), Expert Opinion on Therapeutic Patents, DOI: 10.1080/13543776.2016.1192129

To link to this article: http://dx.doi.org/10.1080/13543776.2016.1192129

Accepted author version posted online: 08 Jun 2016.
Published online: 08 Jun 2016.

Publisher: Taylor & Francis
Journal: *Expert Opinion on Therapeutic Patents*
DOI: 10.1080/13543776.2016.1192129

Review

Small molecules and antibodies for the treatment of psoriasis: a patent review (2010-2015)

Andrea Chiricozzi[1], Rosita Saraceno[2], Lucia Novelli[3], Monika Fida[4], Francesco Caso[5,6], Raffaele Scarpa[5], Luisa Costa[5], Roberto Perricone[3], Marco Romanelli[1], Sergio Chimenti[2]*, Maria Sole Chimenti[3]

[1] Dermatology Department, University of Pisa, Pisa, Italy.

[2] Dermatology Unit, Department of Internal Medicine, University of Rome Tor Vergata

[3] Rheumatology, Allergology and Clinical Immunology, Department of Internal Medicine, University of Tor Vergata, Rome, Italy

[4] University Hospital Center Tirana, Tirana, Republic of Albania

[5] Rheumatology Unit, Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy.

[6] Rheumatology Unit, Department of Medicine DIMED, University of Padua, School of Medicine and Surgery

*** Corresponding author:**

Sergio Chimenti

Dermatology Unit, University of Rome Tor Vergata

Viale Oxford 81, 00133, Rome, Italy

Tel: +39.06.20902742

Fax: +39.06.20902743

E-mail: chimenti@dermatologica.it

Abstract

Introduction: Psoriasis is a chronic condition whose therapeutic armamentarium is increasingly being discussed, particularly when compared to past decades. The use of biologic agents has profoundly changed the history of this disease, as well as the management of psoriatic patients. Due to the enormous interest in psoriasis, as demonstrated within the scientific community and pharmaceuticals, new therapeutic targets have been identified and novel patented therapeutics are being tested.

Areas covered: This review sought to give an overview of small molecules and antibodies patented in the last five years for the treatment of psoriasis. Therapeutic agents either in the early or advanced phase of development have been described, primarily based on a systematic search using the Pubmed Medline database.

Expert opinion: Though the recent introduction of new antipsoriatic agents has facilitated the management of long-term psoriasis, there is still a strong desire for alternative therapeutic options. Indeed, there remain unmet needs regarding safety and efficacy of psoriasis treatment that should be addressed. In this context, recently patented drugs may prove valid, interesting, and promising within the therapeutic paradigm.

Key words: psoriasis, pathogenesis, small molecules, biologic, TNF-±, JAK-STAT

Article highlights

- Although biologic therapies profoundly modified the management of psoriasis, still unmet needs remain.
- Novel patented drugs are being tested for the treatment of psoriasis, both small molecule agents and biologicals.
- Intracellular signaling molecules (JAK-STAT, PDE4, A3 adenosine receptor, S1P, and aka activating protein 1) as well as soluble mediators (i.e. IL-23, IL-17, VEGF-A), receptors (i.e., IL-17R), and surface costimulator molecules (i.e., CD6) have been recognized as therapeutic targets.
- Conceptually, bispecific agents could represent a revolutionary approach as current biologic therapeutics target one single molecule.
- The development of more selective and more effective drugs that maintain very high standards of safety, compared to previously approved biologic agents, is the result of an increased understanding in the psoriasis pathogenic mechanism.

1. Introduction

Psoriasis is a chronic skin disorder whose pathogenic mechanism has been deeply investigated in the last three decades, revealing a crucial role of both adaptive and innate immunity. The immune activation may be triggered by various mechanisms including the presence of self-molecules identified as auto-antigens by autoreactive T cells, both CD4+ and CD8+ T cells [1]. However, early steps of the pathogenesis might involve plasmacytoid and myeloid dendritic cells (pDCs and mDCs, respectively) activated by self-DNA or RNA combined with LL-37 or by chemerin [2-5]. Psoriasis skin inflammation is driven by multiple immune circuits amplified by keratinocytes that recruit T cells, neutrophils, DCs, and other immune cells, producing chemokines and AMPs acting as chemoattractans.

Though key-cytokines such as IL-22, TNF±, and IFN-³ drive pathogenic pathways, which resulted upregulated in psoriasis, mounting evidence has proved the crucial role of the IL-23/IL-17 axis [6].

In this setting, multiple therapeutic targets may be identified: chemokines and their receptors, cytokines and their receptors, adhesion molecules, cell surface antigens, transcription factors, and other intracellular signal transducers.

2 Psoriasis pathogenesis: identification of selective therapeutic targets

2.1 Key cells contributing to psoriasis: T cells

Various subtypes of T cells abundantly infiltrate lesional psoriatic skin including ³´ + T cells and CD4+ T cells, localized within the dermis, and CD8+ T cells infiltrating the epidermis [7-9]. Beside activated resident T cells, the psoriatic plaque includes migrating T cells from the blood circulation. These cells reach lesional skin because of the interaction between leukocyte function-associated antigen-1 (LFA-1), a member of ² ₂ integrin family, and intracellular adhesion molecule-1 (ICAM-1), that

plays a critical role not only in mediating cell adhesion and leukocyte transmigration, but also in increasing T-cell receptor signaling.

Distinct T cell subsets contribute to psoriasis phenotype [10]. Specifically, CD4+ T cells producing pathogenic cytokines such as IL-17, IL-22, and IFN^{3}, are identified as Th17, Th22, and Th1, respectively. There are also CD8+ T cells, which are able to produce the same spectrum of cytokines and are named Tc17, Tc22, and Tc1.

2.1.1 γδ+ T cells

These cells have been recently described as important contributors in psoriasis pathogenesis as they were found significantly increased in lesional psoriatic skin compared to healthy controls. Notably, the total number of IL-17+/ ^{3}´+ T cells was higher than ^{3}´- T cells [9]. Furthermore, they are able to produce IL-17 if stimulated by IL-23, as they do express IL-23R as well as CCR6, similarly to other IL-17-secreting T cells [11].

2.1.2 Innate Lymphoid Cells

This newly described immune cell subtype still needs to be fully characterized both morphologically and functionally. Indeed, they are thought as precursors of NK cells, as bearing NK markers (such as NKp44). Functionally, three ILC subtypes may be distinguished based on their cytokine production: ILC1, producing IFN-^{3}, ILC2, producing IL-4, and ILC3, producing IL-17 and IL-22, and expressing IL-23R. This latter subtype is found increased in both blood and lesional skin of psoriatic patients [12].

2.1.3 Plasmacytoid and myeloid DCs

DCs may be considered crucially involved in the early steps of the inflammatory cascade. pDCs express BDCA-2, CD123, HLA-DR, whereas they do not bear CD11c antigen [13]. When stimulated by toll-like receptor agonists or by chemerin they are

able to secrete interferons, particularly IFN-±, a crucial event in the initiation of the inflammatory psoriasis cascade [13].

Dermal myeloid DCs (mDCs), which are greatly increased in lesional psoriatic skin, do express CD11c and they are negative for BDCA1. mDCs might be activated by different triggers which include toll-like receptor (TLR) agonists, and IFN-±. Once they are activated, they may differentiate into highly inflammatory DCs producing TNF±, nitric oxide, IL-20, and the so-called p40 cytokines, IL-12 and IL-23 [14].

Secreting IL-12, they drive the differentiation of IFN-³+ T cells, while producing IL-23, they sustain and amplify an IL-17+ T cell response [15].

2.1.3 Keratinocytes

Keratinocytes are considered the key-responding tissue cells to the cytokine microenvironment as: (i) they proliferate through an altered differentiation process stimulated by mitogenic cytokines such as IL-22, IL-20, IL-19, and IL-24; (ii) they are immunologically active secreting: antimicrobial peptides (i.e., HBD2, LCN2, S100A family, cathelicidins) that act as chemoattractans, cytokines (TNF±, IL-6, IL-1²), and chemokines including CCL20, CXCL-9, -10, -11, and CXCL-8 that stimulate neutrophil recruitment [16,17].

2.2 Transcription factors

Cell activation reflects the upregulation of multiple signaling pathways involving peculiar transcription factors or enzymes, such as Janus kinase-signal transducer and activator of transcription (JAK-STAT), phosphodiesterase (PDE)-4, and sphingosine 1-phosphate (S1P) receptor.

JAK-STAT signaling is considered one of the most important pathways in psoriasis as it transduces intracellular signals induced by a wide array of cytokines and growth factors [18,19]. Particularly, it plays a critical role in mediating inflammatory immune

responses by converting cytokine signals into genomic responses and, thus, regulating immune cell proliferation and differentiation [18,19].

Overall, JAK tyrosine kinases consist in a family of four non-receptor tyrosine kinases, namely JAK1, JAK2, JAK3 and Tyk2 that act in pairs in the intracytoplasmatic portion of the cytokine receptor. JAK signaling is conventionally transduced to an array of transcription activators, the STAT family, that includes 7 members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6 [20]. Because several cytokines such as IFN-±, IFN-³, IL-2, IL-6, IL-12, IL-15, IL-19, IL-20, IL-22, IL-23, and IL-24 involved in psoriasis pathogenesis act through JAK/STAT signaling pathways, its blockade has been recently proved beneficial in clearing psoriasis [21].

Another highly expressed intracellular enzyme is PDE-4 that is found in activated inflammatory cells (i.e. T cells, DCs) as well as skin tissue cells (i.e., keratinocytes) [22]. Additionally, activated lymphocytes express S1P that is a sphingolipid required to exit the lymphoid tissue and enter the bloodstream via a chemotactic gradient [23].

In this crosstalk involving immune and tissue cells, a plethora of therapeutic targets may be identified for emerging, recently-patented drugs. Particularly, key-cytokines, namely TNF± and IL-17, demonstrated to be crucial in mediating the most relevant inflammatory circuits; and intracellular signaling pathway transducers (i.e., JAK-STAT, PDE4, and S1P) are involved in the pathways driving inflammation and/or proliferation. In this review, we will report patent drugs including small molecules and monoclonal antibodies that are being developed and that may represent promising antipsoriatic therapies in the future.

3. Small molecules

The so-called small molecule drugs are characterized by low molecular size. Compared to biologic therapy, their production is less expensive and allow an oral or topical administration. These therapies are able to neutralize the effects of cytokines

or cytokine receptors blocking intracellular targets such as transcriptional factors or enzymes. Moreover, these products could alleviate many of the challenges that are associated with biologics, namely price, difficulty in production, clinical contraindications, method of administration, and difficulty in producing a significantly less expensive counterpart when patents expire.

Several group of small molecules are under evaluation for the treatment of psoriasis including: 1) JAK inhibitors, 2) the PDE 4 inhibitors, 3) A3 adenosine receptor agonists, 4) TNF± inhibitors, 5) S1P agonist, and 6) aka activating protein 1 (AP-1).

3.1 JAK inhibitors

The JAK protein tyrosine kinase family is constituted by cytoplasmic PTKs that play a pivotal role in cytokine signal transduction pathways through association with various cytokine receptors by activation of the latent forms of STATs involved in the pathogenesis of psoriasis.

Protein kinases like JAKs are enzymes, which transfer phosphate groups from adenosine triphosphate (ATP) or guanosine triphosphate to hydroxyl groups of amino acids of their substrates. Tyrosine kinases phosphorylate tyrosine residues and blocking their enzymatic activity has proved to be a successful strategy [24]. JAK1 is involved in the activation of IFN-^{3}, IL-6 and IL-10 receptors. JAK2 primarily associates with hematopoietic receptors, but also with IL-12 and IL-23 receptors. JAK3 is the most specific type as it acts only with receptors that contain the common ^{3} chain (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21), whose signals are crucial for lymphocyte activation, proliferation and function [25-26]. Because JAK3 is crucial in transducing signals of relevant pathogenic cytokines, such as IL-23, the development of small molecule drugs targeting this kinase were thought to have a therapeutic relevance, as subsequently demonstrated in clinical trial phases.

Tofacitinib is an inhibitor of the JAK1 and JAK3 signaling pathway and it is one of the first JAK inhibitors used in humans. It has been reported to be a safe and effective

therapy for ulcerative colitis [26, 27] and rheumatoid arthritis [28,29] and results of the phase II and III studies on psoriasis have been published [30,31]. The phase II dose-ranging study showed that at week 12, PASI75 response (at least 75% improvement of PASI score compared to the baseline) rates were significantly higher for all tofacitinib-treated patients compared with placebo. At week 12, PASI75 response was reached in 67% of patients receiving 15 mg of tofacitinib daily with the most frequently reported adverse events (AEs) represented by upper respiratory tract infection [30]. A phase III, randomized, multicentre, double-dummy, placebo-controlled, 12-week study, tested non-inferiority of tofacitinib 5 mg and 10 mg, compared with high-dose etanercept or placebo. Patients were randomly assigned in a 3:3:3:1 ratio to receive tofacitinib 5 mg or 10 mg BID at about 12 hours intervals, etanercept 50 mg subcutaneously twice weekly, or placebo [31]. Conversely to 5 mg tofacitinib BID, the higher dose, 10 mg BID was non-inferior to etanercept 50 mg twice weekly in terms of PASI 50, PASI 75, and PASI 90 achievement, as well as PGA response [31]. The adverse event rates over 12 weeks were similar for tofacitinib and etanercept. As stated by the Authors, tofacitinib 10 mg twice-daily showed similar efficacy and safety to etanercept in the short-term period investigated (12 weeks). Although, tofacitinib could represent a valid therapeutic option for patients with moderate-to-severe plaque psoriasis, FDA denied the approval for the treatment psoriasis, pausing its development because the higher dose (10 mg) of tofacitinib, which resulted non-inferior to etanercept, arose safety concerns and was not considered to have an adequate risk-to-benefit ratio.

Due to their small molecular size, tofacitinib has also been studied as topical treatment for psoriasis. In a vehicle-controlled phase IIa trial studying a topical tofacitinib ointment formulation, Ports et al. reported the psoriasis patients treated with tofacitinib 2% ointment 1 BID present an improvement in the target plaque severity score at week 4 [32].

Another JAK inhibitor is ruxolitinib that preferentially inhibits JAK1 and JAK2 and it

has been firstly investigated as topical formulation (INCB018424, Incyte) for use in psoriasis [33]. A Phase 2a trial comparing topical INCB018424 0.5%, 1% and 1.5% cream in a double-blind, vehicle-controlled trial was shown to be safe and effective with improvement in total lesion score, PGA and PASI [34].

There are additional JAK inhibitors undergoing investigation for the treatment of moderate-to-severe psoriasis [35], such as baricitinib (INCB-28050/LY3009104), a JAK1 and JAK3 inhibitor, that is being examined in a phase IIb dose ranging study [36].

3.2 PDE4 inhibitors

Apremilast is an orally available, specific inhibitor of PDE-4 that works intracellularly [37]. PDE4 inhibitors have garnered much investigation as potential modulators of inflammatory signaling. Apremilast has demonstrated the ability to reduce cellular expression of pro-inflammatory markers that are usually elevated in psoriatic tissue, such as IL-23 and TNF±, while simultaneously promoting expression of anti-inflammatory mediators such as IL-10 [38, 39]. Apremilast (Otezla®, Celgene Corporation, Summit, New Jersey) was approved by the US FDA for the treatment of patients with moderate to severe plaque psoriasis for whom phototherapy or systemic therapy is appropriate and for the treatment of patients with active PsA at the dosage of 30 mg BID. The investigators found, in a Phase II, multicentre, dose-comparison study involving patients with moderate-to-severe disease, that at week 16, PASI75 was achieved in 29% of patients receiving 20 mg and 41% of patients receiving 30 mg apremilast BID. AEs (96%) were mild or moderate and no apparent effects of apremilast were observed on haematological, urinalysis, serum chemistry, or electrocardiographic tests [40]. Phase III studies investigated the safety and efficacy of the 30 mg BID dose [41]. The preliminary findings from ESTEEM-1, included 844 patients receiving oral apremilast 30 mg BID, reported a PASI75 response of 33% at week 16 compared to the placebo response of 5.3%. ESTEEM 1 is the first phase III study confirming the efficacy of apremilast in terms of PASI score

and in pruritus in which PASI response was maintained over 52 weeks with continued apremilast treatment. Most patients who were re-randomized to placebo and lost PASI75 response regained it after apremilast reinitiation. Interestingly, apremilast has also demonstrated improvements in the signs and symptoms of psoriatic arthritis and improved in nail, scalp psoriasis, physical function in those patients [42]. Overall, safety profile characterizing apremilast is favorable. The most frequently reported AEs were nausea, upper respiratory tract infection, headache and diarrhea, though a few cases of suicidal ideation and behavior were reported in 0.2% (3 of 1441) of apremilast-treated psoriatic arthritis patients (only one case in plaque-type psoriasis patients) [43,44]. Notably, 2 placebo-treated patients committed suicide compared to none in the apremilast group. Moreover, among apremilast-treated phase III patients, 1.0% of patients reported depression or depressed mood (placebo: 0.8%) [43,44].

3.3 A_3 adenosine receptor agonists

A_3 adenosine receptor agonists are (AAr) G protein-coupled receptors that are involved in a variety of intracellular signaling pathways and physiological functions. The natural ligand of AAr receptors is adenosine. AArs are highly expressed in peripheral blood mononuclear cells isolated from patients with psoriasis and the AAr activation with a specific agonist (CF101) downregulates the nuclear factor-ºB signaling pathway, inhibits the proliferation of specific autoreactive T lymphocytes, and induces apoptosis of inflammatory cells [45]. These effects result in the down-regulation of proinflammatory cytokines, such as TNF±, IL-6, and IL-12 [46].

In a Phase II, multicentre, dose-ranging study, patients with moderate-to-severe plaque-type psoriasis were treated with CF101 (1 mg, 2 mg, or 4 mg) or placebo administered orally BID for 12 weeks. In the 2 mg CF101-treated group, a progressive improvement in the mean change from baseline in PASI versus placebo

throughout the study period was observed, with a statistically significant difference at weeks 8 and 12. In this group, 35.3% of the patients achieved PASI50 response; a higher response rate was not achieved. Side effects reported were considered mild [47].

4. Patented biologic agents

The introduction of biologic agents profoundly changed the management of psoriasis and its therapeutic algorithm, particularly in the long-term treatment. Biologics are mainly represented by monoclonal antibodies neutralizing either receptors or soluble mediators (i.e. cytokines), receptor (i.e., cytokine receptor). The first class of biologic agents used in psoriasis is represented by the TNF± inhibitors. An anti-p40 IL-12/23 agent, ustekinumab, has also been approved for the treatment of psoriasis, and other biologic agents targeting the same pathogenic axis will be marketed.

4.1 Anti-IL23 agents

Besides anti-TNF± inhibitors, new agents targeting other steps in the pathogenic cascade of psoriasis have been developed. IL-23 is a central cytokine to the pathogenesis of psoriasis, its main immunologic role is the involvement in the differentiation process of naïve Th cells into Th17. IL-23 might be targeted by: 1) anti-p40 agents such as ustekinumab, approved for the treatment of plaque-type psoriasis and psoriatic arthritis, and briakinumab (abt-874), another fully humanized antibody that reached a pre-registration status but its development has been discontinued because of the increased incidence in US of major cardiovascular events occurring in briakinumab-treated patients; 2) anti-p19 agents like tildrakizumab (MK-3222), a fully human IgG1 antibody (Merck) that is in a more advanced status of development compared to the other three agents; and 3) IL-23R-antagonists, which are currently being tested in preclinical studies, although no information yet exists regarding their biochemical structure, the status of

development or pharmacokinetics and pharmacodynamics features [48].

Ustekinumab is a fully human monoclonal antibody which blocks the activity of p40, a protein subunit shared by IL-12 and IL-23 [49, 50]. Ustekinumab demonstrated an extremely favorable safety profile as showed by a meta-analysis reporting that few adverse events associated with the use of etanercept and adalimumab reached statistical significance whereas no adverse events were significantly related to ustekinumab use [51]. Ustekinumab has been approved for the treatment of moderate to severe psoriasis in 2009 by the FDA; its efficacy and safety were assessed in the PHONENIX-1 and PHOENIX-2, double-bind, placebo-controlled, clinical trials through 5 years, in patients with moderate to severe plaque psoriasis [52, 53]. In addition to ustekinumab, briakinumab represents another anti-interleukin-12/23p40 monoclonal antibody [54]. Data on briakinumab are available in controlled phase II and III clinical trials, including two 52-week studies conducted in patients with psoriasis. In these studies, briakinumab treatment resulted in clinically significant improvements in quality of life and work productivity in adults with moderate to severe psoriasis [55].

In another phase III, 12-week study, briakinumab showed higher efficacy when compared to placebo and etanercept in patients with moderate to severe chronic plaque psoriasis [56].

Guselkumab (CNTO 1959, Centocor-Janssen Biotech) is a humanized IgG1 monoclonal antibody targeting IL-23p19 subunit that is now being tested in Phase III clinical trial [57]. Its use has been under investigation for the treatment of palmoplantar pustulosis in a Phase III clinical trial, whereas a Phase I trial evaluating the pharmacokinetic of guselkumab comparing lyophilized and liquid formulations has recently been completed (Table 1).

In a randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and clinical response of guselkumab, IL-23 inhibition with a single dose of guselkumab resulted in clinical responses in patients with moderate-to-severe

psoriasis, suggesting that neutralization of IL-23 alone is a promising therapy for psoriasis [58].

Tildrakizumab is a high-affinity, humanized, IgG1/º, anti-IL-23p19 monoclonal antibody developed for treatment of chronic plaque psoriasis [59]. The safety and efficacy of subcutaneous tildrakizumab has been evaluated in a 3-part, randomized, double-blind, phase II trial conducted in 355 adult subjects with moderate to severe chronic plaque psoriasis [60]. Enrolled subjects received tildrakizumab (5, 25, 100, 200 mg) or placebo, injected subcutaneously at weeks 0 and 4 and every 12 weeks thereafter until week 52. Tildrakizumab was discontinued at week 52 and subjects were followed through week 72. The primary efficacy endpoint was PASI 75 response at week 16. In this phase II trial tildrakizumab demonstrated superior efficacy versus placebo that was maintained up to 52 weeks of treatment and for an additional 20 weeks after cessation of study therapy [60]. It was generally safe and well tolerated. The clinical outcomes reported in the previous study are promising, although they await confirmation in the ongoing, larger Phase III trials. Another anti-p19IL-23 agent that is currently under investigation in phase III trials, is BI-655066 [61]. This monoclonal antibody was investigated for the treatment of moderate-to-severe plaque psoriasis in a Phase I randomize double-blind, placebo controlled clinical trial, the primary objective of this trial was the safety evaluation. Among BI-655066 treated patients (31/39) only four serious adverse events (not considered treatment related) were reported; clinical improvement was reached from week 2 and maintained for up to 66 weeks after treatment) [62].

4.2 Agents targeting IL-17 (secukinumab, brodalumab and ixekizumab)

Th-17 responses include the dysregulation of several cytokines, in particular IL-17A that shows to have a key role in the regulation of innate and adaptive immune pathways [63-65].

IL-17A is an inflammatory cytokine produced by a wide array of immune cells,

including CD4+ T cells, and other innate immune cells such as CD8+ T cells, 3´ T cells, mast cells, and neutrophils, at sites of skin plaques and inflamed entheses [66]. IL-17A, acting with other pro-inflammatory cytokines, including TNF±, leads to up-regulation of expression of different genes associated to inflammatory response in different cells, as well keratinocytes and fibroblasts, leading to increased production of proinflammatory molecules [66]. Additionally, a recent study has shown a possible role of a neutrophil-keratinocyte axis in psoriasis that may involve neutrophil-derived IL-17, representing an early target of IL-17A-directed agents [67]. Several IL-17A inhibitors have shown promising results in several phase II studies, and more recently, in phase III RCTs on psoriasis and PsA.

Secukinumab represents a fully human IgG1º monoclonal antibody, which selectively neutralizes IL-17A [68]. Secukinumab has been investigated more largely in psoriasis and recently obtained the approval, by FDA and EMA, for the treatment of psoriasis and psoriatic arthritis. [69, 70]. Secukinumab has been also tested in Crohn's disease showing poor clinical response (31% of treated patients discontinued treatment prematurely) showed a significant difference in favor of placebo and concerns about its safety profile in treating this condition [71]. Conversely to TNF inhibitors and p40IL-12/IL-23 blockers that may treat both disorders, warnings on secukinumab use in patients with Crohn's disease have been labeled. In the treatment of psoriasis secukinumab was proved effective, as initially observed in two, 52-weeks, phase III randomized, double-blind, placebo-controlled trials, named ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis), and FIXTURE (Full Year Investigative Examination of Secukinumab versus Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis) [72]. Secukinumab demonstrated higher efficacy in treating psoriasis, particularly in achieving PASI 90 and PASI 100 response, compared to both placebo and etanercept. Regarding the safety profile, infection rates including upper respiratory tract infection and nasopharyngitis were higher in patients on secukinumab than placebo group in both

studies, but similar to those seen in the group on etanercept [72]. Similarly, another head-to-head study testing secukinumab versus ustekinumab, demonstrated a higher efficacy of secukinumab as PASI 90, PASI 75, PASI 100, response, and DLQI improvement, compared to ustekinumab [73]. Secukinumab (both 300 mg and 150 mg doses) was also tested as continuous or as-needed regimen showing non-inferiority of retreatment “as needed” vs. fixed doses [74]. Indeed no significant difference were detected comparing the two groups, though PASI 75 response achieved after 12-week secukinumab treatment (84.4%-91.1% of treated subjects) was maintained throughout Week 52, more frequently in the “fixed interval” group (78.2%, 300 mg; 62.1%, 150 mg) compared to “retreatment as needed” group (67.7%, 300 mg; 52.4%, 150 mg). The potential of retreatment as needed with secukinumab warrants further investigation [74].

Other clinical trials and subanalyses confirmed the preliminary data about safety and efficacy of secukinumab both in the short- and long- term [75-79].

Brodalumab (AMG-827) is a fully human IgG2, monoclonal antibody that binds with high affinity IL17AR blocking IL-17A, IL-17E and IL-17F signaling. Clinical trials have been completed in rheumatoid arthritis, Crohn's disease and psoriasis [80,81]. In a Phase III study of patients with moderate-to-severe plaque psoriasis, brodalumab was investigated versus ustekinumab and versus placebo [82]. Eighty-six percent of the patients in the brodalumab 210 mg group achieved at least 75% improvement in disease severity compared to baseline after 12 weeks, whereas 70% of patients in the ustekinumab arm and 8.1% of patients in the placebo arm achieved 75% improvement [82]. However, based on reports of suicidal thoughts and behavior during clinical trials, brodalumab development has been halted and a re-evaluation of the safety profile is being processed in order to rule out these safety warnings.

Ixekizumab (LY-2439821) is a IgG4 humanized anti-IL17 monoclonal antibody, which has been evaluated in a phase II, double-blind, placebo-controlled trial involving patients with chronic plaque psoriasis with scores of at least 12 on PASI [83,84].

Patients received subcutaneous injections of 10, 25, 75 or 150 mg of ixekizumab or placebo at 0, 2, 4, 8, 12 and 16 weeks. The primary endpoint was the proportion of patients with a reduction in PASI score by at least 75% at 12 weeks. Secondary endpoints included the proportion of patients with a reduction in the PASI score by at least 90% or by 100% [84]. At 12 weeks, the percentage of patients with a reduction in PASI75 was significantly greater with ixekizumab 150 mg (82.1%), 75 mg (82.8%), and 25 mg (76.7%), than with placebo (7.7%), as was the percentage of patients with a reduction in the PASI score by at least 90%: 150 mg (71.4%), 75 mg (58.6%), and 25 mg (50%) versus placebo [84]. Similarly, a 100% reduction in the PASI score was achieved in significantly more patients in the 150 mg group (39.3%), and the 75 mg group (37.9%) than in the placebo group (0%). Adverse events occurred in 63% of patients in both the combined ixekizumab groups and in the placebo group. The most common adverse events were upper respiratory infections, injection-site reactions and headache. No serious adverse events or major cardiovascular events were observed. The results of this study demonstrated that neutralization of IL-17 with ixekizumab may be an effective treatment for patients with chronic moderate-to-severe plaque psoriasis [84]. Recently, ixekizumab received the approval for the treatment of moderate-to-severe plaque psoriasis by FDA.

5. Bi-specific monoclonal antibodies

Conventionally, therapeutic monoclonal antibodies selectively recognize one target. Because psoriasis pathogenesis identified multiple mediators playing a crucial role, novel therapeutics targeting more than one mediator could be more effective [85]. Inflammation is one of the histopathological aspects characterizing psoriasis together with epidermal hyperplasia and neoangiogenesis, thus the neutralization of two targets at the same time may exclusively affect the inflammatory process as occurs blocking both IL-17 and TNF±, or blocking both vascular endothelial growth factor (VEGF) and TNF±, the inhibition of neoangiogenesis and inflammation may be

induced.

Fynomers are small binding proteins (7 kDa) derived from the human Fyn SH3 domain. Fyn is a tyrosine-specific phospho-transferase that is a member of the Src family of tyrosine protein kinases Fynomers can be engineered to bind to any target of interest with high affinity and specificity [86,87]. In a study published in 2014 a fynomer inhibiting *in vitro* IL-17A was developed (Fynomer 2C1) [88]. Fynomer 2C1 was genetically fused to the Fc part of a human antibody via four different amino acid linkers to yield bivalent binding proteins; the 2C1-Fc fusion protein with the longest linker displayed the most potent anti-IL17 inhibitory activity. Furthermore, in the same study it has been shown that in a mouse model of acute inflammation, the most potent 2C1-Fc fusion protein was able to efficiently inhibit IL-17A *in vivo*. According to these evidences, Fynomer-Fc fusion proteins represent new drug candidates for the treatment of IL-17A mediated inflammatory conditions including psoriasis [89].

Recently, a novel drug called Valpha, which is a chimeric fusion protein inhibiting both VEGF and TNF± simultaneously, has been tested in a mouse model of psoriasis [90]. Valpha showed superior relief effects in a psoriasis model with regard to epidermal thickness and the area of blood and lymphatic vessels. Thus, the simultaneous blocking of VEGF-A and TNF± using Valpha could be an effective therapeutic strategy for psoriasis [91].

Together with TNF±, another cytokine, namely IL-17A, is recognized as central to the development and progression of inflammatory diseases. Therapeutics, which are able to simultaneously inhibit TNF± and IL-17A, represent the next generation of biologic agents and they are expected to be more effective than current monospecific therapies.

The FynomAb COVA322 (Covagen Pharmaceuticals) is one of them. It consists of a fully human, clinically validated anti-TNF± antibody and anti-IL-17A fynomers, genetically fused to C-terminal light-chains of the antibody [92]. COVA322 inhibits with picomolar potency TNF± and IL-17A at the same time. COVA322 is currently

under investigation in a Phase Ib/IIa clinical trial in patients with stable chronic moderate-to-severe plaque psoriasis (Table 1).

6. Other targets

Itolizumab is a novel humanized monoclonal antibody which targets CD6, a T-cell costimulator molecule, involved in T cells proliferation, signaling, gene expression and cytokines secretion [93, 94].

Itolizumab resulted effective and safe for the treatment of moderate-to-severe chronic plaque psoriasis, in a 52-week phase III, double-blind, randomized, placebo-controlled, parallel-arm, multicenter clinical trial, performed in twenty centers across India [95]. Two-hundred and twenty-two patients were randomized (2:2:1) to two different itolizumab arms A or B. The arm A received a 4-week loading dose of 0.4 mg/kg/wk followed by 1.6 mg/kg every 2 weeks. The arm B received 1.6/mg every 2 weeks. The arm C received placebo. At week 12, the placebo arm was switched to 1.6 mg/kg itolizumab every 2 weeks. The primary end point was the proportion of patients with at least 75% improvement in PASI score at week 12 [95]. The main secondary assessment was PGA. Quality-of-life assessments were also performed, using SF-36 and DLQI. Histopathology was evaluated: T-cell infiltration, rete thickness, and epidermal thickness in psoriatic lesions were measured. T cells were visualized in 7- to 8-µm sections using antihuman CD3 staining. One-hundred and ninety-nine patients (88.4%) completed week 28 and one-hundred and seventy-one patients (76.0%) completed the entire study (until week 52). Other than PASI score less than 50 at week 28, the common reasons for withdrawal were lost to follow-up (10 [4.4%]), withdrawal of consent (7 [3.1%]), and disease progression or relapse (7 [3.1%]). Five patients (2.2%) withdrew for adverse events (mostly, infusion reactions) [95]. A total of 27.0% in arm A, 36.4% in arm B, and 2.3% in arm C met the primary end point (achieved a PASI75 response at week 12) [95]. The difference from placebo was statistically significant (P = .0172 for A and .0043 for B). The induction

regimen (arm A) did not demonstrate additional benefit. Improvement was seen in arm C after crossover to itolizumab at week 12 [95]. Responders continued to increase in arms A and B from week 12 to week 28. Improvements over placebo were seen for T-cell infiltration and epidermal thickness at week 12, and in all arms at week 28.

Itolizumab showed comparable efficacy to existing therapies, excellent safety, and measurable improvements in quality of life [95].

7. Conclusion

Psoriasis is a debilitating disorder whose treatment has been profoundly modified by the identification of different therapeutic targets: cytokines and their receptors, cell surface antigens, transcription factors, and other intracellular signal transducers. The first one to be effectively targeted was TNF±. More recently, cytokines sharing the p40 subunit, namely IL-12 and IL-23, were thought to play an important role in psoriasis leading to the development of the antibodies targeting p40. As the pathogenesis of psoriasis evolved and the importance of the IL-23/IL-17 axis has emerged, at least three antibodies targeting IL-17 or its receptor have been clinically tested. Thus, advances in both knowledge and drug development led to new therapies that are more selective and more effective, maintaining very high standards of safety compared to previously approved biologic agents. Antibodies Therapeutic monoclonal antibodies or fusion proteins neutralizing cytokines, cytokine subunits, or receptors will represent part of the future therapeutic armamentarium that will be completed by small molecule drugs.

8. Expert opinion

Psoriasis vulgaris is a chronic condition wherein effective and safe therapies are needed for long-term use. Treatments available for psoriasis have rapidly increased

in recent years. Nevertheless, many of them may have serious side effects, in particular in the long-term. Being a chronic condition, a favorable long-term safety and efficacy profile should represent the most critical hallmark for an antipsoriatic agent. New advances in the understanding of psoriasis pathogenesis led to the development of new drugs that are produced through biotechnology. These products seem to be more effective and safe for long-term compared to conventional therapies. There will be several new options for the treatment of psoriasis in the upcoming years. Patented drugs and, the therapeutic paradigm will be further expanded by the emerging targets herein reported that have not been long enough studied to ascertain any uncommon AEs and long-term efficacy that may be associated with these new agents.

Because, PASI 90 and PASI 100 are currently considered a successful therapeutic response, the primary goal of the latest patented monoclonal antibodies is clearing skin, reaching a PASI score improvement of at least 90% with respect to baseline PASI [96]. Particularly, the anti-IL-17 agents obtained a strikingly high clinical response in treating psoriasis, showing superior efficacy compared to marketed biologic agents. This superiority has been convincingly demonstrated by various head-to-head trials testing anti-IL-17 agents versus either a TNF inhibitor (etanercept) or an anti-p40 agent (ustekinumab). The introduction of anti-IL17 drugs in clinical practice bears the promise of achieving at least PASI90 response in a consistent portion of treated patients.

Notably, neither TNF± nor IL-17 blockers are able to obtain a satisfactory response in 100% of patients. This evidence may have important implications as it might represent the result of alternative pathogenic circuits that are not driven by the targeted mediator. Thereby, newest therapeutic antibodies neutralizing more than one cytokine may have the advantage of contemporarily blocking multiple key steps of the pathogenic cascade conversely to one-cytokine-blocking antibody. As previously showed, IL-17 and TNF± synergistically act in mediating the key

inflammatory circuits in psoriasis [16], thus, it would be of interest testing the efficacy of these antibodies bispecific for both IL-17 and TNF±. On the other hand, small molecules will not have the same efficacy as biologics, but they show some important advantages: they are orally available and easier to produce. According with their mechanism of action, small molecules could potentially expand the oral treatment armamentarium for psoriasis, either as monotherapy or combined with topical, systemic or biologic therapies. It would be of interest to study combinations of small molecules with other antipsoriatic therapeutics. Considering the therapeutic armamentarium available and the future therapeutic scenario, biosimilars need to be mentioned, though they are off-patented drugs. Biosimilars show an identical primary amino acid sequence, dose, route of administration, compared to the originators, whose patent expired. They need to prove comparable pharmacokinetics, pharmacodynamics, safety and efficacy with the reference products. Nevertheless, the clinical development program is usually smaller compared to a new biologic agent because comparability trials may be performed on a smaller and “sensitive” study population, and the originator’s indications may be extrapolated. By definition, biosimilars cannot give any advantage (except for the price) compared to their originators; otherwise they would represent “biobetter” products with significant implications in terms of drug development, as they would be considered as a brand-new agent. Thereby, the introduction of biosimilars will not expand the antipsoriatic drug array but it will affect health care costs. Among biosimilar class of TNF-agents, infliximab biosimilars are actually available in the market. Pharmaceutical companies received approval for their infliximab biosimilar in Europe in September 2013 and it has been approved by EMA for the same indications as Remicade (inflixmab), i.e. ankylosing spondylitis, Crohn’s disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis. Since small molecular differences (i.e., glycosylation) may affect safety and immunogenicity, tracking of adverse events associated with the use of both reference and biosimilar products, and the ability to readily identify the

manufacturer and the product name is an issue that must be addressed.

Undoubtedly, the introduction of new-patented drugs blocking in a different manner a well known key-player in psoriasis or targeting alternative mediators (i.e., guselkumab, apremilast, tofacitinib, ixekizumab) could definitely represent a relevant benefit and support to treat patients non-responders or contraindicated to current antipsoriatic therapies. Preliminary data from multiple clinical trials suggested that higher selectivity in blocking the IL-23/IL-17 axis reflects greater efficacy maintaining a favourable safety profile. A straightforward example is provided by a head-to-head study recently presented at the last American Academy of Dermatology testing an anti-p19IL-23 agent (BI-655066) vs. an anti-p40IL-12/IL-23 agents (ustekinumab). The sharper neutralization of IL-23 activity by BI-655066, avoiding the suppression of IL-12 signalling, obtained higher clinical response in terms of PASI 90, PASI 100, and static Physician Global Assessment (sPGA), compared to ustekinumab [97]. Limited long-term clinical data for certain drugs, and the complete lack of clinical outcomes for the bispecific biologic agents, do not allow the definition of the future therapeutic paradigm. Likely, the introduction of IL-17 blockers will increase the opportunity to treat patients, providing an important chance not only for biologic-naïve patients, but also to those unresponsive to the current biologic drugs. To the light of recent and forthcoming approvals for various therapeutics, including apremilast, tildrakizumab, and guselkumab, and considering the future bispecific molecules approaching a later phase of development, the traditional therapeutic algorithm will profoundly change and it is difficult, now, to be defined.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Reference annotations

* Of interest

** Of considerable interest

1. Lande R, Botti E, Jandus C, et al. The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. Nat Commun. 2014; 5: 5621.

□□ First publication demonstrating the presence of autoreactive T cells in psoriasis

2. Albanesi C, Scarponi C, Pallotta S, et al. Chemerin expression marks early psoriatic skin lesions and correlates with plasmacytoid dendritic cell recruitment. J Exp Med 2009;206:249-58

□□ One of the suggested primum movens in the pathogenic mechanism of psoriasis.

3. Ganguly D, Chamilos G, Lande R, et al. Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. J Exp Med 2009;206:1983-94

□□ One of the suggested primum movens in the pathogenic mechanism of psoriasis.

4. Lande R, Ganguly D, Facchinetti V, et al. Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. Sci Transl Med 2011;3:73ra19

5. Nestle FO, Conrad C, Tun-Kyi A, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med 2005;202:135-43

□□ Crucial role of plasmacytoid DCs in psoriasis.

6. Lowes MA, Russell CB, Martin DA, Towne JE, Krueger JG. The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. Trends Immunol. 2013; 34: 174-81

7. Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol. 2008;128:1207-11.

8. Hijnen D, Knol EF, Gent YY, Giovannone B, Beijn SJ, Kupper TS, et al. CD8(+) T cells in the lesional skin of atopic dermatitis and psoriasis patients are an important source of IFN-g, IL-13, IL-17, and IL-22. J Invest Dermatol. 2013;133:973-9

9. Cai Y, Shen X, Ding C, et al. Pivotal role of dermal IL-17-producing gammadelta T cells in skin inflammation. Immunity 2011;35:596-610

10. Chiricozzi A. Pathogenic role of IL-17 in psoriasis and psoriatic arthritis. Actas Dermosifiliogr. 2014; 105: 9-20.

11. Mabuchi T1, Takekoshi T, Hwang ST. Epidermal CCR6+ ³´ T cells are major producers of IL-22 and IL-17 in a murine model of psoriasiform dermatitis. J Immunol. 2011; 187: 5026-31.

12. Teunissen M, Munneke M, Bernink J, et al. Composition of innate lymphoid cell subsets in the human skin: Enrichment of NCR. ILC3 in lesional skin and blood of psoriasis patients. J Invest Dermatol 2014;134:2351–60

13. Nestle FO, Conrad C, Tun-Kyi A, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med 2005;202:135-43

□□ Crucial role of plasmacytoid DCs in psoriasis.

14. Lowes MA, Chamian F, Abello MV, et al. Increase in TNF-alpha and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). Proc Natl Acad Sci USA 2005;102:19057-62

□□ Central role of Tip DCs in psoriasis.

15. Tonel G, Conrad C, Laggner U, et al. Cutting edge: A critical functional role for IL-23 in psoriasis. J Immunol. 2010;185:5688-91.

16. Chiricozzi A, Guttman-Yassky E, Suárez-Fariñas M, et al. Integrative responses to IL-17 and TNF-a in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. J Invest Dermatol. 2011;131: 677-87.35.

□□ Article describing the key inflammatory circuits contributing to psoriasis

17. Chiricozzi A, Nograles KE, Johnson-Huang LM, et al. IL-17 induces an expanded range of downstream genes in reconstituted human epidermis model. PLoS One.

2014; 9: e90284.

18. Leonard WJ, O'Shea JJ. Jaks and STATs: biological implications. Annu Rev Immunol 1998; 16: 293-322

19. Igaz P, Toth S, Falus A. Biological and clinical significance of the JAK-STAT pathway; lessons from knockout mice. Inflamm Res 2001; 50: 435-41

20. Shuai K, Liu B. Regulation of JAK-STAT signalling in the immune system. Nat Rev Immunol 2003;3(11):900-11

21. Chiricozzi A, Faleri S, Saraceno R, et al. Tofacitinib for the treatment of moderate-to-severe psoriasis. Expert Rev Clin Immunol. 2015; 11: 443-55

22. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. Biochem Pharmacol. 2012; 83: 1583-90.

23. Cyster JG. Chemokines, sphingosine-1-phosphate, and cell migration in secondary lymphoid organs. Annu Rev Immunol. 2005; 23: 127-59.

24. Kaminska B, Swiatek-Machado K. Targeting signaling pathways with small molecules to treat autoimmune disorders. Expert rev Clin Immunol. 2008; 4: 93–112.

25. Seavey MM, Dobrzanski P. The many faces of Janus kinase. Biochem Pharmacol 2012; 83(9):1136-45

26. Pesu M, Candotti F, Husa M, et al. Jak3, severe combined immunodeficiency, and a new class of immunosuppressive drugs. Immunological reviews. 2005; 203:127–42.

26. Pfizer. Crystalline and non- crystalline forms of tofacitinib, and a pharmaceutical composition comprising tofacitinib and a penetration enhancer. WO2012137111A1. 2012

27. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med. 2012; 16;367(7):616-24.

28. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6): 495-507.

29. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab

versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.

30. Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. Br J Dermatol 2012; 167: 668–677.

31. Bachelez H, van de Kerkhof PC, Strohal R, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet 2015; 386(9993):552-61.

32. Ports WC, Khan S, Lan S, et al. A randomized phase 2a efficacy and safety trial of the topical Janus kinase inhibitor tofacitinib in the treatment of chronic plaque psoriasis. Br J Dermatol 2013;169(1):137-45. 2013;169(1):137–145

33. Concert pharmaceuticals inc. Deuterated derivatives of ruxolitinib WO2013188783A1. 2013

34. Punwani N, Scherle P, Flores R, et al. Preliminary clinical activity of a topical JAK1/2 inhibitor in the treatment of psoriasis. J Am Acad Dermatol. 2012;67(4):658-64.

35. Ortiz-Ibanez K, Alsina MM, Munoz-Santos C. Tofacitinib and other kinase inhibitors in the treatment of psoriasis. Actas Dermosifiliogr. 2013;104(4):304-10

36. Abbvie Inc. Jak1 selective inhibitor and uses thereof. US20150118229A1. 2015

37. Celgene corp. Methods and compositions using pde4 inhibitors for the treatment and management of autoimmune and inflammatory diseases. WO2012149251A1. 2012

38. Schafer PH, Parton A, Gandhi AK, et al. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. Br J Pharmacol 2010; 159: 842–855

39. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. Biochem Pharmacol 2012; 83: 1583–1590.

40. Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. Lancet 2012; 380: 738–

746.

41. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). Am Acad Dermatol. 2015; 73(1):37-49.

42. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomized, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014; 73:1020-1026.

43. http://www.otezla.com/otezla-prescribing-information.pdf

44. Busa S, Kavanaugh A. Drug safety evaluation of apremilast for treating psoriatic arthritis. Expert Opin Drug Saf. 2015; 14(6):979-85.

45. Can-Fite Biopharma Ltd. Pharmaceutical composition comprising a3 adenosine receptor agonist (ib-meca/cf-101) for treatment of psoriasis. WO2011027348A1. 2011

46. Fishman P, Bar-Yehuda S, Liang BT, Jacobson KA. Pharmacological and therapeutic effects of A3 adenosine receptor agonists. Drug Discov Today. 2012; 17: 359–366.

47. David M, Akerman L, Ziv M, et al. Treatment of plaque-type psoriasis with oral CF101: data from an exploratory randomized phase 2 clinical trial. J Eur Acad Dermatol Venereol 2012; 26: 361–367.

48. Chiricozzi A, Saraceno R, Chimenti MS, et al. Role of IL-23 in the pathogenesis of psoriasis: a novel potential therapeutic target? Expert Opin Ther Targets. 2014; 18(5):513-25.

49. Yeilding N, Szapary P, Brodmerkel C, et al. Development of the IL-12/23 antagonist ustekinumab in psoriasis: past, present, and future perspectives--an update. Ann N Y Acad Sci 2011; 1222:30–9.

50. Bartlett BL, Tyring SK. Ustekinumab for chronic plaque psoriasis. Lancet 2008; 371(9625):1639–40.

51.Sorenson E and Koo J. Evidence-based adverse effects of biologic agents in the treatment of moderate-to-severe psoriasis: Providing clarity to an opaque topic. J Dermatolog Treat. 2015; 26(6):493-501

52. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from arandomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371(9625):1665–74.

53. Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007; 356(6):580–92.

54. ABBVIE INC. Methods for treating psoriasis by administering an antibody which binds an epitope of the p40 subunit of IL-12 and/or IL-23. US9051368B2. 2015.

55. Langley RG, Papp K, Gottlieb AB, et al. Safety results from a pooled analysis of randomized controlled phase II and III clinical trials and interim data from an open-label extension trial of the interleukin-12/23 monoclonal antibody, briakinumab, in moderate to severe psoriasis. J Eur Acad Dermatol Venereol 2013;27:1252-61.

56. Papp KA, Sundaram M, Bao Y, et al. Effects of briakinumab treatment for moderate to severe psoriasis on health-related quality of life and work productivity and activity impairment: results from a randomized phase III study. J Eur Acad Dermatol Venereol 2014; 28 (6):790-8.

57. Merck Sharp & Dohme. Crystalline anti-human IL-23 antibodies. WO2014004436A2. 2014

58. Sofen H, Smith S, Matheson RT, et al. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol. 2014; 133(4):1032-40.

59. Merck Sharp & Dohme Corp. IL-23 antagonists for treatment or prevention of skin rash associated with treatment with p13k/akt pathway inhibitors. WO2013009535A1. 2013

60. Papp K, Thaçi D, Reich K, et al. Tildrakizumab (MK-3222), an Anti- IL-23p19 Monoclonal Antibody, Improves Psoriasis in a Phase 2b Randomized Placebo-Controlled Trial. Br J Dermatol 2015;173(4):930-9.

61. Barrett Rabinow, Jane O. Werling; Baxter International Inc., Baxter Healthcare Sa. Methods And Compositions For Reducing Pain, Inflammation, And/Or Immunological Reactions Associated With Parenterally Administering A Primary Therapeutic Agent. US20150024031 A1. 2015

62. Krueger JG, Ferris LK, Menter A, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2015; 136(1):116-124.

63. Kirkham BW, Kavanaugh A, Reich K. Interleukin-17A: a unique pathway in immune-mediated diseases: psoriasis, psoriatic arthritis and rheumatoid arthritis. Immunology. 2014;141:133-42

64. Chiricozzi A, Guttman-Yassky E, Suárez-Fariñas M, et al. Integrative responses to IL-17 and TNF-± in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. J Invest Dermatol. 2011; 131(3): 677-87.

65. Chiricozzi A, Krueger JG. IL-17 targeted therapies for psoriasis. Expert Opin Investig Drugs. 2013; 22 (8): 993-1005.

66. Lynde CW, Poulin Y, Vender R, et al. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol. 2014;71:141-50.

67. Reich K, Papp KA, Matheson RT, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. Exp Dermatol. 2015;24:529-35.

68. NOVARTIS AG. Methods of treating psoriasis using IL-17 antagonists. WO2012045848A1. 2012.

69. Novelli L, Chimenti MS, Chiricozzi A, Perricone R. The new era for the treatment of psoriasis and psoriatic arthritis: Perspectives and validated strategies. Autoimmun

Rev 2014;13(1):64-9.

70. Chiricozzi A. Pathogenic role of IL-17 in psoriasis and psoriatic arthritis. Actas Dermosifiliogr. 2014; 105 (1): 9-20.

71. Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut. 2012; 61(12):1693-700.

72. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014; 371:326-38.

73. Thaçi D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol. 2015;73:400-9.

74. Mrowietz U, Leonardi CL, Girolomoni G, et al. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). J Am Acad Dermatol. 2015;73:27-36.

75. Ohtsuki M, Morita A, Abe M, et al. Secukinumab efficacy and safety in Japanese patients with moderate-to-severe plaque psoriasis: subanalysis from ERASURE, a randomized, placebo-controlled, phase 3 study. J Dermatol. 2014; 41:1039-46.

76. Paul C, Reich K, Gottlieb AB, et al. Secukinumab improves hand, foot and nail lesions in moderate-to-severe plaque psoriasis: subanalysis of a randomized, double-blind, placebo-controlled, regimen-finding phase 2 trial. J Eur Acad Dermatol Venereol. 2014;28:1670-5.

77. Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015; 29:1082-90.

78. Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety, and usability results from a randomized controlled trial in Psoriasis (FEATURE). Br J Dermatol. 2015; 172:484-93

79. Thaçi D, Humeniuk J, Frambach Y, et al. Secukinumab in psoriasis: randomized, controlled phase 3 trial results assessing the potential to improve treatment response in partial responders (STATURE). Br J Dermatol. 2015; 173:777-87.

80. Mease PJ, Genovese MC, Mutebi A, et al. Improvement in Psoriasis Signs and Symptoms Assessed by the Psoriasis Symptom Inventory with Brodalumab Treatment in Patients with Psoriatic Arthritis. J Rheumatol. 2016; 43(2):343-9.

81. Barber, J. Amgen, Astra Zeneca's brodalumab meets primary endpoints of third Phase III trial in moderate-to severe-plaque psoriasis. First Word Pharma, 2014. Web. 2015.

82. Bauer E, Lucier J, Furst DE. Brodalumab -an IL-17RA monoclonal antibody for psoriasis and psoriatic arthritis. Expert Opin Biol Ther 2015;15(6):883-93.

83. Corning Inc. Delamination resistance pharmaceutical glass containers containing active pharmaceutical ingredients. US2014341888A1. 2014.

84. Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med 2012;366(13):1190–9.

☐ First publication on ixekizumab therapy for psoriasis

85. Kanakaraj P, Puffer BA, Yao XT, et al. Simultaneous targeting of TNF and Ang2 with a novel bispecific antibody enhances efficacy in an in vivo model of arthritis. MAbs. 2012;4(5):600-13.

86. Binz HK, Amstutz P, Plückthun A. Engineering novel binding proteins from nonimmunoglobulin domains. Nat Biotechnol 2005; 23(10):1257-68.

87. Gebauer M, Skerra A. Engineered protein scaffolds as next generation antibody therapeutics. Curr Opin Chem Biol. 2009; 13(3):245-55.

88. Covagen Ag. Il-17 binding compounds and medical uses thereof - US20130005659A1. 2013

89. Silacci M, Baenziger-Tobler N, Lembke W, et al. Linker length matters, fynomer-

Fc fusion with an optimized linker displaying picomolar IL-17A inhibition potency. J Biol Chem. 2014; 289(20):14392-8.

90. JUNG KEEHOON. Fusion protein capable of binding vegf-a and tnf-alpha. US8927232B2. 2015

91. Jung K, Lee D, Lim HS, et al. Double anti-angiogenic and anti-inflammatory protein Valpha targeting VEGF-A and TNF-alpha in retinopathy and psoriasis. J Bilo Chem. 2011; 286(16):14410-8.

92. Covagen AG. A novel fusion protein comprising an antibody light chain and a polypeptide binding to IL-17. EP2597102A1. 2013.

93. Biocon LTD. Use of a CD6 binding partner and method based thereon. WO2015011658A1. 2015

94. Nair P, Melarkode R, Rajkumar D, Montero E. CD6 synergistic co-stimulation promoting proinflammatory response is modulated without interfering with the activated leucocyte cell adhesion molecule interaction. Clin Exp Immunol 2010; 162:116-30.

95. Krupashankar DS, Dogra S, Kura M, et al. Efficacy and safety of itolizumab, a novel anti-CD6 monoclonal antibody, in patients with moderate to severe chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, phase-III study. J Am Acad Dermatol 2014; 71(3):484-92.

96. Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. J Eur Acad Dermatol Venereol. 2015; 29(4):645-8.

97. K Papp et al. 2015. Efficacy and safety of different dose regimens of a novel selective IL-23p19 inhibitor (BI 655066) compared with ustekinumab in patients with moderate-to-severe plaque psoriasis. 73rd Annual Meeting of the American Academy of Dermatology, San Francisco, California, 20-24th March 2015 [Presentation].

Table 1. Therapeutic agents patented in 2010-2015.

Agent	Description	Phase of Development for psoriasis	Patent
Tofacitinib	JAK1 and JAK3 inhibitor	Phase III	WO2012137111A1 (2012)[26]
Ruxolitinib	JAK1 and JAK2 inhibitor	Phase III	WO2013188783A1 (2013)[33]
Baricitinib	JAK1 and JAK3 inhibitor	Phase IIb	US20150118229A1 (2015)[36]
Apremilast	PDE-4 inhibitor	Marketed by FDA	WO2012149251A1 (2012)[37]
CF101	A_3 adenosine receptor agonist	Phase III	WO2011027348A1 (2011)[43]
Fynomer 2C1	Fynomer inhibiting IL-17A	Pre-clinical	US20130005659A1 (2013)[52]
Valpha	Bispecific chimeric fusion protein inhibiting VEGF and TNF±	Pre-clinical	US8927232B2. (2015)[54]
COVA322	Bispecific fynomer inhibiting TNF± and IL-17A	Phase II	EP2597102A1 (2013)[56]
Briakinumab (ABT-874)	Anti-interleukin-12/23p40 monoclonal	Development discontinued (phase III)	US9051368B2 (2015)

	antibody		
Guselkumab (CNTO 1959)	Anti-IL-23p19 subunit monoclonal antibody	Phase III	WO2014004436A2 (2014)[65]
Tildrakizumab	Anti-IL-23p19 subunit monoclonal antibody	Phase III	WO2013009535A1 (2013)[66]
Secukinumab	Anti-IL-17 monoclonal antibody	Pre-marketing	WO2012045848A1 (2012)[72]
Brodalumab (AMG-827)	IL17AR blocking monoclonal antibody	Phase III	WO2011046958A1 (2011)[83]
Ixekizumab (LY-2439821)	Anti-IL17 monoclonal antibody	Phase III	US2014341888A1 (2014)[86]
Itolizumab	CD6 blocking monoclonal antibody	Phase III	WO2015011658A1 (2015)[88]