In recent years, the increased understanding of the pathophysiology of psoriasis has resulted in several new treatments. The success of ustekinumab proved the importance of the IL-23/T helper cell 17 axis in psoriatic diseases. Several new biologics targeting this axis will reach the clinic in the next years. Biologics are costly, require injections, and some patients experience taphylaxis, thus, the development of orally available, small-molecule inhibitors is desirable. Among small-molecules under investigation are A3 adenosine receptor agonists, Janus kinase inhibitors, and phosphodiesterase inhibitors. We review published clinical trials, and conference abstracts presented during the last years, concerned with new drugs under development for the treatment of psoriasis. In conclusion, our psoriasis armamentarium will be filled with several new effective therapeutic options the coming years. We need to be aware of the limitations of drug safety data when selecting new novel treatments. Monitoring and clinical registries are still important tools. Key words: psoriasis; ustekinumab; secukinumab; ixekizumab; brodalumab; apremilast; tofacitinib.

Accepted Aug 11, 2014; Epub ahead of print Aug 11, 2014

Acta Derm Venereol 2015; 95: 133–139.

Kristian Kofoed, Department of Dermato-allergology, Gentofte Hospital, University of Copenhagen, Niels Andersens Vej 65, DK-2900 Hellerup, Denmark. E-mail: kristian.kofoed@regionh.dk

In recent decades, understanding of the pathophysiology of psoriasis has changed from that of an intrinsic epidermal keratinocyte disease to a T-cell-mediated disease to now being considered a systemic inflammatory disease with an evident role for the immune system (1). This has been reflected in changes in treatment modalities over the years, starting with non-selective treatments such as corticosteroids, methotrexate, and acitretin, and moving on to more selective treatments such as cyclosporine and the highly selective biological therapies (2). The introduction of tumour necrosis factor (TNF)-α inhibitors resulted in a breakthrough in the management of moderate-to-severe psoriasis and changed our understanding of psoriasis pathophysiology. The achievement of the TNF-α inhibitors is also reflected in the annual sales. In 2013, the 3 best-selling prescription drugs in the world were adalimumab, etanercept and infliximab, generating annual sales of approximately US$ 10 billion. Because these drugs are also used to treat other inflammatory conditions, e.g. rheumatoid arthritis and Crohn’s disease, the total number of psoriasis patients treated with a TNF-α inhibitor is not known. Another method of treating psoriasis has been the targeting of T cells, either via inhibition of the binding of lymphocyte function-associated antigen-3 (LFA-3) to CD2 (e.g. with alefacept) or via blocking of the CD11a chain of LFA-1 and inhibition of cell adhesion (e.g. with efalizumab). However, in Europe, alefacept was never approved and efalizumab was withdrawn because of serious side-effects (3). The only other major antipsoriatic drug with a specific physiological target that has been introduced is the interleukin-12/23 (IL-12/23) monoclonal antibody, ustekinumab (4). The success of ustekinumab proved the importance of the IL-23/T helper cell 17 (Th17) axis in psoriatic diseases, and several new biologics targeting this axis will probably reach the clinic in coming years (5). Ustekinumab is only labelled for treatment of psoriasis and psoriatic arthritis. In 2013 annual sales reached US$ 1.5 billion.

The biologics are not only costly, they also require repeated injections and some patients experience a loss of therapeutic effect (i.e. taphylaxis). Thus, the development of orally available, small-molecule inhibitors that are less expensive to produce is desirable. Several small molecules are under investigation for the treatment of psoriasis. The first ones that potentially will be approved are tofacitinib, a Janus kinase (JAK) inhibitor, and apremilast, a phosphodiesterase inhibitor. Other small molecules investigated are A3 adenosine receptor agonists and new anti-inflammatory agents (6).

In this article we give an overview of new biologics and small molecules under development for the treatment of plaque psoriasis. We will review the clinical trials published in peer-reviewed journals since 2011, and the significant conference abstracts presented in 2013 and 2014 that are concerned with small molecules and biologics under development for the treatment of psoriasis. The emphasis of this review article is on the mechanisms of action, efficacy, and adverse effects of these new agents.

NEW BIOLOGICS

Interleukin-12/23 inhibitors

IL-12 and IL-23 are heterodimeric pleiotropic cytokines each consisting of 2 subunits that are named...
were similar to AEs in the placebo group. Results from this group showed that after 16 weeks of treatment 74% of patients achieved a PASI75 compared with 4.4% in the placebo group. AEs were reported in 66% of patients receiving guselkumab and 72% of patients receiving adalimumab; 3% and 5% reported at least one serious AE in these respective groups. One guselkumab-treated patient reported a malignancy (cervical intra-epithelial neoplasia III). Three MACE were reported in guselkumab-treated patients, all of whom had multiple pre-existing cardiovascular risk factors.

Interleukin-17 inhibitors

The members of the IL-17 family include IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F (5, 9). All members of the IL-17 family have a similar protein structure with 4 highly conserved cysteine residues critical to their tertiary structure and have little sequence similarity to any other known cytokines (5, 8, 9). IL-17A is a key “driver” pro-inflammatory cytokine in psoriasis pathogenesis (5). It can activate keratinocytes leading to hyperproliferation and further production of antimicrobial peptides, cytokines, and chemokines, which, in turn, recruit and activate other immune cells leading to amplification of psoriasis inflammation (5). Several IL-17 inhibitors are under investigation for use in psoriasis (Fig. 1 and Table I).

Secukinumab is a human IgG1κ monoclonal antibody that selectively binds and neutralises IL-17A. A Phase II study has shown that 12 weeks of treatment of patients with moderate-to-severe psoriasis with subcutaneous secukinumab resulted in significantly higher PASI75 response rates compared with placebo (82% vs. 9%; p < 0.001). The PASI90 response rate was 52% at week 12 compared with 5% in the placebo group. In general, secukinumab was well-tolerated but 2 cases of neutropenia (both grade 2 or lower) were reported in the cohort (13). At the 22nd Congress of the European Association of Dermatology and Venereology (EADV) in October, 2013 (Istanbul, Turkey), the results of the head-to-head Phase III FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept using 2 Dosing Regimens to Determine Efficacy in Psoriasis) study were presented3. More than half (54%) of secukinumab-treated patients achieved a PASI90 at week 12, compared with 21% of etanercept-treated patients. A PASI100 at week 12 was seen in 24% of the secukinumab group versus 4% of the etanercept group. Secukinumab efficacy was sustained over the full one-year of treatment in the FIXTURE study (14).


New psoriasis drugs

A PASI90 response at week 52 was observed in 65% of patients. There were no major safety signals identified.

Ixekizumab is a humanised IgG4 monoclonal antibody that also neutralises IL-17A. At 12 weeks, the percentage of patients with moderate-to-severe psoriasis who had a PASI75 or PASI90 was 82% and 71%, respectively, in the groups receiving subcutaneous ixekizumab. AEs occurred in 63% of patients across the ixekizumab groups and in the placebo group. No serious AEs or major cardiovascular events were observed.

Brodalumab works in a slightly different way to the other IL-17 inhibitors as it is a human antibody that acts as an antagonist to the receptor subunit shared by the IL-17A, IL-17F, and IL-17A/F heterodimer ligands. A Phase II study assigned patients with psoriasis to receive subcutaneous brodalumab. At week 12, PASI75 and PASI90 was seen in 82% and 75%, respectively. The most commonly reported AEs in the patients receiving brodalumab were nasopharyngitis (8%), upper respiratory tract infection (8%), and injection site erythema (6%) (15).

Based on results from published trials, the IL-17 inhibitors seem to have fast-acting positive effects in patients with moderate-to-severe psoriasis. By week 12 of treatment, a PASI75 response was achieved in at least 82% of patients in all trials. The 3 agents even led to a high number of patients with a PASI90 response with no major side-effects. However, longer-term studies are needed as inborn errors of IL-17 immunity lead to chronic mucocutaneous candidiasis in humans (16).

Anti-tumour necrosis factor agents

Although the concept of blocking TNF-α to treat psoriasis is already established, a new anti-TNF antibody called certolizumab pegol has been introduced. This is a polyethylene glycol-conjugated TNF inhibitor, which unlike other anti-TNF monoclonal antibodies (e.g. infliximab and adalimumab) lacks a fragment crystallizable (Fc) portion and, consequently, does not induce antibody-dependent cytotoxicity, complement activation, or apoptosis in T cells or macrophages. The reduced risk of such inflammatory events could potentially make re-treatment safer. Similarly to infliximab and adalimumab, certolizumab pegol binds to soluble and membrane-bound TNF-α, thus blocking crucial events associated with inflammation in psoriasis.

Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved certolizumab pegol for the treatment of ankylosing spondylitis, rheumatoid arthritis, and psoriatic arthritis. Certolizumab pegol has been tested in a Phase II study involving 176 patients with moderate-to-severe psoriasis. PASI75 was achieved by 83% of patients in the certolizumab pegol 400 mg group. Most side-effects were mild or moderate and were consistent with those reported for TNF inhibitors in previous trials. Serious AEs occurred in 3% and 5% in the two certolizumab pegol groups (400 mg certolizumab pegol at baseline, then either 400 mg or 200 mg once every 2 weeks for 10 weeks), and in 2% in the placebo group (17).
Table I. New psoriasis therapies being tested

<table>
<thead>
<tr>
<th>Drug name (ref)</th>
<th>Active substance</th>
<th>Target</th>
<th>Efficacy</th>
<th>Common side-effects</th>
<th>Current status</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tildrakizumab (13)</td>
<td>IgG1 monoclonal antibody IL-23 p19 subunit</td>
<td>NA</td>
<td>Phase III completed</td>
<td>El Lilly</td>
<td>Novartis</td>
<td>Phase III completed</td>
</tr>
<tr>
<td>Ustekinumab (15, 16)</td>
<td>IgG4 monoclonal antibody IL-17A</td>
<td>Week 4: reduction in least square mean 54% vs. vehicle 42%</td>
<td>Phase II completed</td>
<td>UCB</td>
<td>Phase III completed</td>
<td></td>
</tr>
<tr>
<td>Certolizumab pegol (20)</td>
<td>IgG2 monoclonal antibody Fab: fragment antigen-binding</td>
<td>NA</td>
<td>Phase II completed</td>
<td>Pfizer</td>
<td>Phase III completed</td>
<td></td>
</tr>
<tr>
<td>Brodalumab (18)</td>
<td>IgG2 monoclonal antibody</td>
<td>IL-17A</td>
<td>Phase III completed</td>
<td>Can-Fite BioPharma</td>
<td>Phase III completed</td>
<td></td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Small molecule Inhibitor of JAK1 and JAK3 signalling pathway</td>
<td>NA</td>
<td>Phase III completed</td>
<td>Amgen</td>
<td>Phase III completed</td>
<td></td>
</tr>
<tr>
<td>Apremilast</td>
<td>Small molecule Inhibitor of JAK1 and JAK3 signalling pathway</td>
<td>NA</td>
<td>Phase III completed</td>
<td>Pfizer</td>
<td>Phase III completed</td>
<td></td>
</tr>
<tr>
<td>Ixekizumab (17)</td>
<td>IgG4 monoclonal antibody IL-17A</td>
<td>Week 12: PASI75 82%, PASI90 71%</td>
<td>Phase II completed</td>
<td>Incyte</td>
<td>Phase III completed</td>
<td></td>
</tr>
<tr>
<td>CE-787/F0020</td>
<td>Small molecule Inhibitor of JAK1 and JAK3 signalling pathway</td>
<td>NA</td>
<td>Phase III completed</td>
<td>Pfizer</td>
<td>Phase III completed</td>
<td></td>
</tr>
<tr>
<td>CF101 (36)</td>
<td>Small molecule A3 adenosine receptor (A3AR) agonist</td>
<td>NA</td>
<td>Phase II completed</td>
<td>Can-Fite BioPharma</td>
<td>Phase III completed</td>
<td></td>
</tr>
<tr>
<td>Ruxolitinib (34)</td>
<td>Small molecule Inhibitor of JAK1 and JAK2 signalling pathway</td>
<td>NA</td>
<td>Phase III completed</td>
<td>Amgen</td>
<td>Phase III completed</td>
<td></td>
</tr>
</tbody>
</table>

Effects were observed on the results of haematological, urinalysis, serum chemistry, or electrocardiographic tests (22). Eight serious AEs occurred (placebo, n = 3; apremilast 20 mg, n = 3; apremilast 30 mg, n = 2), but none were judged to be related to apremilast treatment (22).

Among established TNF inhibitors, several biosimilar products will probably be licensed in the coming years. A biosimilar is defined as a biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product. Thus, biosimilars made by different manufacturers are not identical to the original product or each other, unlike generic drugs. Minor differences are expected and permitted as long as any such differences are demonstrated not to be clinically meaningful (18). The patents of a growing number of biologic drugs have already expired or are due to expire, which has led to an increased interest in the development of biosimilars. In September 2013, the EMA approved Inflectra™, the first infliximab biosimilar, and an etanercept biosimilar, CHS-0214, has shown comparable pharmacokinetics with etanercept in a pivotal clinical study (19).

**SMALL MOLECULES**

Several small molecules are under investigation for psoriasis treatment, including phosphodiesterase (PDE) inhibitors, JAK inhibitors, and A3 adenosine receptor (A3AR) agonists.

**Phosphodiesterase inhibitors**

PDE-4 is an enzyme that catalyses the breakdown of 3’-5’-cyclic adenosine monophosphate (cAMP) to AMP (20). cAMP is known to downregulate inflammation and the increase of its concentration associated with PDE-4 inhibition will reduce the production of pro-inflammatory mediators that are involved in psoriasis, such as TNF-α and IL-23, and increase the production of anti-inflammatory mediators, such as IL-10 (20, 21). Apremilast is an orally available, small-molecule, specific inhibitor of PDE-4 that works intracellularly (20). Apremilast was approved by the FDA in March 2014 for treatment of adults with active psoriatic arthritis. In a Phase II, multicentre, dose-comparison study involving patients with moderate-to-severe psoriasis, the investigators found that at week 16, a PASI75 was achieved in 29% of patients receiving 20 mg and 41% of patients receiving 30 mg apremilast twice daily (22). For both groups, the differences in response compared with the placebo group were significant (p < 0.001). Most AEs (96%) were mild or moderate and no apparent effects of apremilast were observed.
and 25% of those patients who had failed prior TNF blocking therapies had a PASI75 response. In this short study, there were no cases of tuberculosis or lymphoma and no increases in cardiovascular risk or opportunistic infections. Intestinal intolerance, a well-known adverse event with PDE-4 inhibitors, was reported (diarrhoea and nausea for apremilast vs. placebo, 18.8% and 15.7% vs. 7.1% and 6.7%, respectively). Gastrointestinal AEs occurred mostly within the first 15 days of the first dose and most cases resolved within a further 15 days.1

Janus kinase inhibitors

JAKs are cytoplasmic protein tyrosine kinases (TYKs) that are essential for the initiation of cytokine-activated signalling pathways. JAKs are linked to the phospho-signalling pathways. JAKs are cytoplasmic protein tyrosine kinases (TYKs) that are essential for the initiation of cytokine-activated


_A3_ adenosine receptor agonists

_A3_ ARs are G protein-coupled receptors that are involved in a variety of intracellular signalling pathways and physiological functions. The natural ligand of A3AR receptors is adenosine. Targeting an A3AR to combat inflammation is based on two findings. Firstly, A3ARs are highly expressed in peripheral blood mononuclear cells isolated from patients with psoriasis (30). Secondly, A3AR activation with a specific agonist (CF101) downregulates the nuclear factor-κB signalling pathway, inhibits the proliferation of specific autoreactive T lymphocytes, and induces apoptosis of inflammatory cells (30). These effects result in the down-regulation of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-12 (30).

In a Phase II, multicentre, dose-ranging study, 75 patients with moderate-to-severe plaque-type psoriasis were enrolled and treated with CF101 (1 mg, 2 mg, or 4 mg) or placebo administered orally twice daily for 12 weeks (31). In the 2 mg CF101-treated group, a progressive improvement in the mean change from baseline in PASI vs. placebo throughout the study period was observed, with a statistically significant difference at weeks 8 and 12 (p = 0.047 and p = 0.031, respectively) (31). In this group, 35.3% of the patients achieved a PASI50 response, and 23.5% of the patients achieved a Physician Global Assessment (PGA) score of 0 or 1 (graded on a 0–5 scale). Side-effects reported from the study with CF101 were mild. Only 4 patients were withdrawn from the study because of AEs, including one patient in the placebo group (31).

Based on the studies published to date, small molecules will not have the same efficacy as biologics, however, they possess some important advantages. They are orally available or can even be used in topical formulations, they are less expensive to produce, and they may provide important new insights into the pathophysiology of psoriasis.

DISCUSSION

Multiple new drugs are under investigation for the treatment of psoriasis, targeting different extracellular and intracellular immune processes. Some of these new drugs have demonstrated excellent clinical effects in trials, even when looking at the PASI90 response. There will be several new options for the treatment of psoriasis in coming years, however, it is evident that the trials reviewed here have not been long enough or large enough to ascertain any uncommon AEs that may be associated with these new agents. The upcoming Phase III trials will provide important new information, but even these trials will not be able to identify rare AEs or elucidate the long-term safety, as the experience with efalizumab development demonstrated. Based on studies in approximately 2,700 patients, efalizumab was approved for the treatment of moderate-to-severe psoriasis in 2003. In 2009, the drug was withdrawn from the market as 3 confirmed and one suspected case of spontaneous progressive multifocal leukoencephalopathy (PML) were reported after more than 46,000 patients were exposed to efalizumab (3). All 4 patients had been on monotherapy with efalizumab for over 3 years and worldwide only 1,100 patients had similarly been treated for 3 years. Because PML is very rare, it is extremely unlikely that the 4 reported cases were caused by chance and, knowing that PML primarily occurs in immunosuppressed patients, the association is likely causal. The acknowledgment of PML as a very serious, but statistically rare, risk associated with efalizumab treatment, demonstrates the weaknesses of the current drug approval and pharmacovigilance processes for fully measuring the safety of a drug (3). Clinicians need to be aware of the relative limitations of existing safety data of a drug when selecting a treatment. Careful monitoring and large clinical registries are and will continue to be important tools to detect these rare AEs.

All of the new treatment options highlight the need for head-to-head studies. It is also desirable that therapies are evaluated in clinically complex psoriasis patient groups, such as patients with comorbidities. These individuals more closely resemble those seen in the daily clinical setting compared with the highly selected patient groups involved in drug approval studies. Furthermore, studies that consider different psoriasis subtypes, patient outcomes, genetic backgrounds, and biomarker behaviours are needed. Another shortcoming of the short-term nature of most clinical studies is the lack of information regarding the propensity of the new monoclonal antibodies to induce an antibody response, which may limit their long-term effectiveness.

This review covered only published clinical trials, however, there are several other drugs under clinical investigation for the treatment of psoriasis. The results of these studies such as that of the selective sphingosine 1-phosphate receptor 1 agonist, ponesimod, which protects against lymphocyte-mediated tissue inflammation (32), are yet to be published.

CONCLUSION

Our psoriasis treatment armamentarium is likely to be filled with several new, effective, therapeutic options over the coming years. These new treatments are helping us to better understand the pathophysiology of psoriasis. However, we need to be aware of the limitations of drug safety data when selecting a treatment, therefore, careful monitoring and large clinical registries are still important tools in patient care.

ACKNOWLEDGEMENT

Conflicts of interest: KK has received fees as a speaker from AbbVie, Janssen-Cilag, Merck Sharp & Dohme and Pfizer and has served as an advisory board member for AbbVie. LS has
received consultancy and/or speaker honoraria from Abbott, Pfizer, Janssen-Cilag, MSD and Leo Pharma, is a member of the Advisory Boards of MSD, Novartis, Abbvie and Janssen-Cilag and has participated as investigator in clinical trials with MSD, Novartis, Abbvie and Amgen. CZ has received consultancy and/or speaker honoraria from Abbott, Pfizer and Takeda and is a member of the Advisory Boards of AbbVie, Novartis, Eli Lilly, MSD and Janssen-Cilag.

REFERENCES