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New Therapeutic Agents for Psoriasis

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ABSTRACT

During the last decades, inside and deep knowledge of the pathogenesis of psoriasis, has led to new therapeutic agents for the treatment of the disease, resulting in a revolutionary and holistic therapeutic approach. For many years the anti-TNF agents as well as the agents that target the IL12/23 pathway, have changed the armamentarium of drugs in the treatment of psoriatic disease with excellent results. In the present article we will present all available data about new agents that are under development for the treatment of psoriasis, like anti-IL17 and anti-IL23 biologics, as well as the small molecules, like JAK inhibitors and inhibitors of phosphodiesterase-4 (PDE4).

KEYWORDS Psoriasis; IL-17 Inhibitors; IL-23 Inhibitors; PDE4 Inhibitors; Small Molecules; JAK Inhibitors.

INTRODUCTION

During the last decades, new targeted therapeutic agents for the treatment of psoriasis are available, the biologic agents. Three anti-TNF-a agents are available (adalimumab, etanercept, infliximab) and one antiIL-12/23 drug (ustekinumab). All these drugs have long-term high efficacy for the treatment of psoriasis, increased safety profile and low toxicity. The advantage of biologics is the concurrent very good control, not only of psoriasis, but also of all the other comorbidities that are related with psoriasis, like psoriatic arthritis (all four agents mentioned above are indicated also for psoriatic arthritis). Another important advantage is the luck of organ toxicity with biologics, compared with the well-known toxicity of either cyclosporine or methotrexate after long-term use. There are many reports in the literature about the protective role of anti-TNF agents against cardiovascular events and especially myocardial infarction.

New drugs are under development or have recently been approved for the treatment of psoriasis, like IL-17, IL-23, phosphodiesterase-4 (PDE4) and JAK inhibitors.

1. IL-17 inhibitors

1.1 Secukinumab

It is a fully human antibody against IL-17A [1]. Secukinumab has recently been approved and is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic treatment. The approved dosage is 300 mgr subcutaneously in weeks 0-4 and once monthly thereafter. ERASURE και FIXTURE are the two studies on which the approval has been based on [2].

In the ERASURE study, double-blind phase, two different doses of Secukinumab where compared (150 and 300 mgr, once weekly for 5 doses and once monthly thereafter), with placebo. At week 12, the percentage of patients who achieved PASI (Psoriasis Area Severity Index) 75 was 81. 6% (with 300 mgr Secukinumab), 71. 6% (with 150 mgr Secukinumab) και 4.5% (with placebo) [3].

Moreover, PASI 90 was achieved in 59.2% and 39.1% of patients under 300 and 150 mgr Secukinumab, respectively, compared with 1.2% of patients under placebo. With regards to IGA (Investigator's Global Assessment) 0/1 index (almost or total clearance of psoriasis) at week 12, the percentages were 65.3%, 51.2% και 2.4% for 300, 150 mgr Secukinumab and placebo, respectively.

In the FIXTURE study, Secukinumab (150 and 300 mgr, once weekly for 5 doses and once monthly thereafter) was compared with Etanercept (50 mgr twice weekly for 12 weeks and 50 mgr once weekly thereafter), with placebo.

With regards to PASI 75 at week 12, the percentage of patients who achieved PASI 75 was 77.1% (300 mgr Secukinumab), 67% (150 mgr Secukinumab), 44% (etanercept) and 4.9% (placebo). In 4.7% and 2.3% of patients under Secukinumab

(300 and 150 mgr respectively), mild Candida infections were reported and the percentage for Etanercept patients was 1.2%. 3rd grade neutropenia was reported in 1% of patients under Secukinumab, with 0 cases in the etanercept group. IL-17A is implicated in the innate immunity against Candida albicans and in some haemopoiesis pathways.3 Up to now there is no safety concern about these two parameters and Secukinumab. All Candida infections were mild and only topical or in a few cases systematic antifungal treatment was needed, without being necessary to discontinue Secukinumab in any case. Neutropenia was also not important in all cases as well.

1.2 Ixekizumab

It is a humanized IgG4 monoclonal antibody against IL-17A. A phase 2, double-blind, compared with placebo study, reports at week 12 achievement of PASI 75 in 82.1% of patients under Ixekizumab 150 mgr, 82.8% under 75 mgr, 76.7% under 25 mgr against 7.7% under placebo (the administration of drug was performed at weeks 0, 2, 4, 8, 12 and 16, subcutaneously) [4].

Ixekizumab was compared with Etanercept (in studies phase III UNCOVER 2, 3) [5]. At week 12 (UNCOVER 2), patients under Ixekizumab achieved PASI 75 in a percentage of 90% (administration every 2 weeks), 78% (administered every 4 weeks), compared with 42% under etanercept and 2% under placebo. In UNCOVER 3 these percentages were 87%, 84%, 53% and 7%, respectively.

1.3 Brodalumab

It is a fully human antibody against the receptor of IL-17 (IL-17A και IL-17F). Brodalumab was compared with placebo in a phase III study (AMAGINE-1) and the results of efficacy with regards to PASI 75 at week 12 were 83.3%, 60.3% and 2.7% for doses of Brodalumab 210mgr and 140 mgr every two weeks subcutaneously and placebo, respectively. In studies AMAGINE 2 and 3, Brodalumab was compared to Ustekinumab and to placebo [6]. At week 12 the percentage of patients who achieved a PASI 75 improvement was 86% and 67% for Brodalumab dose of 210 mgr and 140 mgr respectively, in comparison with 70% for Ustekinumab and 8% for placebo (AMAGINE 2) [7]. In AMAGINE 3 study, the results were 85.1%, 69.2%, 69.3% and 6%, respectively.

In May 2015, all studies of Brodalumab for psoriasis were paused, worldwide, because of some cases of suicidal ideation and change of behaviour in patients who received Brodalumab [8].

2. IL-23 inhibitors

2.1 Tildrakizumab

It is a humanized IgG1 monoclonal antibody that blocks the p19 subunit of IL-23. The drug was compared with placebo in a phase 2b study with primary endpoint PASI 75 at week 16 [9]. Patients were randomized in 5 groups with doses of 200, 100, 25, 5 mgr Tildrakizumab or placebo. The results for PASI 75 were 74%, 66%, 64% and 33% for Tildrakizumab and 4.9% for placebo, respectively. The most common adverse event was rhinofaringitis. At the time that this paper is written, phase III clinical trials are under development.

2.2 Guselkumab

It is a human monoclonal IgG1 antibody against the p19 subunit of IL-23. In a double-blind phase I study, the drug was compared to placebo. One dose of 10 mgr was administered to 5 patients, one dose of 30 mgr to 5 patients, one dose of 100 mgr to 5 more and 300 mgr to 5 patients also. Placebo was administered to 4 patients. At week 12, the percentage of patients that achieved PASI 75 was 50%, 60%, 60%, 100%, respectively, for the four doses of guselkumab and 0% for placebo [10].

The drug was also compared with adalimumab in a phase II study with a 52-week duration. 293 patients were randomized to receive either Guselkumab 5 mgr at weeks 0, 4 and every 12 weeks thereafter, 15 mgr every 8 weeks, 50 mgr at weeks 0, 4 and every 12 weeks thereafter, 100 mgr every 8 weeks or 200 mgr at weeks 0, 4 and every 12 weeks thereafter, until week 40, or placebo, or adalimumab (with the administration program that is indicated for psoriasis). At week 16, the placebo group patients were initiated guselkumab 100 mgr every 8 weeks. The primary endpoint was the evaluation of PGA 0 or 1 at week 16. The results regarding this index were 34% for 5-mg guselkumab group, 61% for 15-mg group, 79% for 50-mg group, 86% for 100-mg group and 83% for 200-mg group, compared with 7% for the placebo group. The percentage for adalimumab was 58% [11].

3. Small molecules

3.1 Apremilast

It is a small molecule inhibitor of PDE4. It has been recently approved for the treatment of psoriatic arthritis as either monotherapy or in combination with DMARDs, in adult patients who have an inadequate response or are tolerant to previous treatment with DMARDs. It has also been recently approved for the treatment of moderate to severe plaque type psoriasis in adult patients who have failed to respond or have a contraindication or are intolerant to systemic conventional therapies (including cyclosporine, methotrexate or PUVA). The dose is 30 mgr twice daily peros, with an escalation dose (10 mgr the 1st day, 10 mgr twice daily for the 2nd day, 30 mgr the 3rd day, 40 mgr the 4th day, 50 mgr the 5th day and 60 mgr from the 6th day and thereafter. The safety and efficacy of apremilast in psoriasis have been evaluated in 2 multicenter, randomized, double-blind, controlled with placebo, trials (ESTEEM 1 και ESTEEM 2) [12, 13].

In both trials, patients have been randomized 2:1 in 30 mgr apremilast twice daily or placebo for 16 weeks and after this period, from week 16 until week 32, all patients received 30 mgr apremilast twice daily. In both trials, the primary endpoint was the number of patients who achieved PASI 75 at week 16. In ESTEEM 1, 33.1% of patients under apremilast had a PASI

75 at week 16 compared with 5.3% of the placebo group. In ESTEEM 2, these numbers were 28.8% and 5.8%, respectively. The secondary endpoint was the percentage of patients that had sPGA (static PGA) 0 or 1 (total or almost clearance) at week 16. In ESTEEM 1, 21.7% of patients achieved this target compared with 3.9% of the placebo group and the results for ESTEEM 2 were 20.4% and 4.4%, respectively.

4. Jακ Inhibitors

4.1 Tofacitinib

It is a small molecule inhibitor of Jακ-1/Jακ-3. Janus kinases are a family of intracellular tyrosine kinases that connect different receptors with intracellular pathways. There are 4 members of the JAK family: Jακ-1, Jακ-2, Jακ-3 and tyrosine kinase 2.

Two phase III trials have investigated the efficacy of tofacitinib in comparison with placebo, for moderate to severe plaque type psoriasis [14]. Regarding PASI 75 at week 16, 59.4%, 43.1% και 8.9% were the number of patients that reached this target for tofacitinib (taken orally) 10 mgr bid, 5 mgr bid and placebo, respectively. Regarding clearance or almost clearance of psoriasis (PGA 0 or 1), these numbers were 59.1%, 44% and 10%, respectively. Tofacitinib was also compared with etanercept from Bachelet et al. PASI 75 efficacy at week 12 was evaluated and the results were 63.6% for tofacitinib 10 mgr twice daily (orally), 58.8% for etanercept 50 mgr twice weekly subcutaneously, 39.5% for tofacitinib 5 mgr twice daily and 5.6% for placebo[15].

CONCLUSION

Many new and promising drugs are either under development or have recently been approved for the treatment of psoriasis. In the present manuscript only drugs that are either in phase II or in phase III clinical trials or have recently been indicated for psoriasis are reported. Every day clinical practice and long term safety remain to be evaluated in the future for these agents.

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