

Could Anti IL12/23 Therapy Replace Anti-TNF Biologics?

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SUMMARY Biologic therapies improved dramatically the outcome of psoriatic arthritis and moderate to severe chronic plaque psoriasis. Anti-TNF agents were developed approximately one decade ago by rheumatologists and today represent one of the most effective classes of drugs in severe psoriasis resistant to 2 out of 3 "classic" systemic therapies (methotrexate, cyclosporine, and PUVA). Recent studies on psoriasis pathogenesis were focused on early steps of the inflammatory cascade, i.e. activation of T cells with a recently described phenotype Th17 and consequent expression of interleukins (IL) 12 and 23. IL12 and IL23 have a common p40 subunit that is a target of a new therapeutic class, fully human monoclonal antibodies anti IL12/23: ustekinumab and ABT-874. Randomized, placebo-controlled clinical trials in patients with moderate to severe chronic plaque psoriasis using ustekinumab and ABT-874 showed PASI 75 achievements at week 12 in 80% and 93% of patients, respectively. Larger studies are ongoing in order to assess the safety profile of this new therapy. As anti-TNF drugs represent an important and effective treatment of psoriatic arthritis and moderate to severe plaque psoriasis, comparative studies are needed to assess the advantages, the safety and the place of anti-IL12/23 in the era of biologic therapy.

KEY WORDS: plaque psoriasis, anti IL 12/23 therapy, ustekinumab, ABT-874, anti TNF-alpha therapy

INTRODUCTION

Psoriasis is a chronic inflammatory disease with an incidence of 3% to 5% in general population, with severe forms accounting for 20% of psoriasis cases (1). Systemic treatment is indicated in psoriatic arthritis and in moderate to severe forms of psoriasis (2). The traditional treatment of psoriasis recommends a stepwise approach to treatment starting with topical agents, followed by phototherapy, then systemic agents.

First-line systemic therapies prescribed today for moderate to severe plaque psoriasis include acitretin, phototherapy (psoralene-ultraviolet A, PUVA, and narrowband UVB 311 nm), methotrexate, and cyclosporine. Patients with no response (or having contraindications) to 2 of 3 first-line systemic therapies (phototherapy and/or methotrexate and/or cyclosporine) have an indication for biologic therapy ("biologics"). These new molecules

have dramatically improved the outcome of patients not responding to usual systemic therapies. Anti-TNF therapies are immunomodulators targeting TNF alpha and were developed approximately one decade ago by rheumatologists, today representing one of the most effective classes of drugs in severe psoriasis resistant to 2 out of 3 "classic" systemic therapies. The main anti-TNF agents approved in the European Community for psoriatic arthritis and moderate to severe plaque psoriasis are etanercept (fusion protein), infliximab (chimeric monoclonal antibody), and adalimumab (fully human monoclonal antibody) (3,4) (Fig. 1).

The risk of severe adverse events (SAEs) occurring in psoriasis patients treated with biologics (alefacept, efalizumab, etanercept and infliximab) was evaluated in a retrospective study using relative risk (RR) and number needed to harm (NNH), and was increased in alefacept (RR=1.09; P=0.03; NNH=15), efalizumab (RR=1.15; P<0.001; NNH=9) and infliximab groups (RR=1.18; P<0.001; NNH=9) as compared with placebo. SAEs were increased in sensitivity analysis of four efalizumab trials (n=2443; RR=1.92; P=0.03; NNH=60) (5). Efalizumab, a monoclonal antibody targeting T cell (anti CD11a), was withdrawn from European market in March 2009.

TARGETING IL12/IL23

Recent studies on the pathogenesis of psoriasis were focused on early steps of inflammatory cascade, i.e. activation of T cells to Th1 phenotype and a recently described Th17 phenotype, with consequent expression of interleukins (IL) 12 and 23 (6). IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells such as macrophages and dendritic cells.

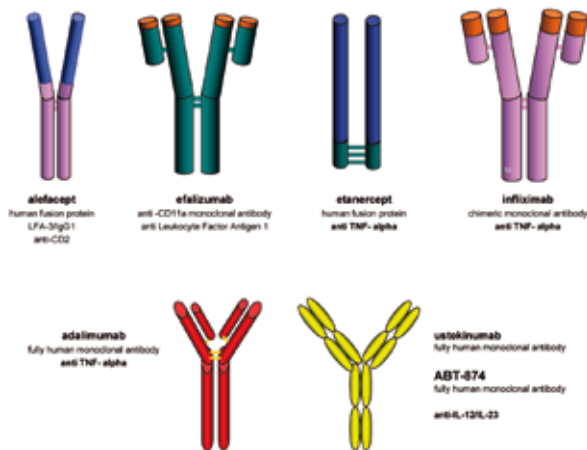


Figure 1. Main biologic treatments for psoriasis.

Abnormal regulation of IL-12 and IL-23 has been associated with immune-mediated diseases such as psoriasis. IL-23 supports chronic inflammation by maintaining a separate CD4+ T cell subset characterized by IL-17 production. Recently, Th17 subset has been shown to elaborate IL-22, which mediates IL-23-induced dermal inflammation and epidermal hyperplasia in mice (7). IL-23 is thought to maintain and expand Th17, which is characterized by the production of IL-17 and IL-22 (7). Moreover, in a study on 1810 psoriatic patients and 2522 control subjects, psoriasis was associated with the polymorphism of IL23B and IL23R haplotype (8). IL12 and IL23 have a common p40 subunit, which is a target of two new fully humanized monoclonal antibodies belonging to the same class, anti-IL12/23: ustekinumab and ABT-874. Recent clinical trials showed the anti-IL12/23 ustekinumab and ABT-874 to be effective in moderate to severe plaque psoriasis (9-11).

In the physiopathology of psoriasis, IL-6, TGF-β, IL12 and IL23 play important roles in T-cell differentiation from naive T cell (Tn) to Th1 or Th17 phenotype (6) (Fig. 2). A "psoriasis risk gene set" was found in association with HLA Cw6, IL12B, IL23R and IL-13 (12). Ustekinumab down regulated gene expression of inflammatory cytokines such as TNF-alpha, MCP-1 and IL-8 in lesional skin biopsies (7). The same pleiotropic susceptibility loci linked to IL12 and IL23 were identified in patients with Chron's disease and in those with psoriasis (13,14). The structure of IL12 and IL23 presents an identical subunit, p40 (Fig. 3), a target of the monoclonal antibodies ustekinumab (8,9) and ABT-874 (11).

Phase III studies with the human monoclonal antibody anti IL12/23 ustekinumab (9,10) and phase II studies with the human monoclonal antibody anti IL12/23 ABT-874 (11) were conducted in series of patients with clinically stable, moderate to severe plaque psoriasis.

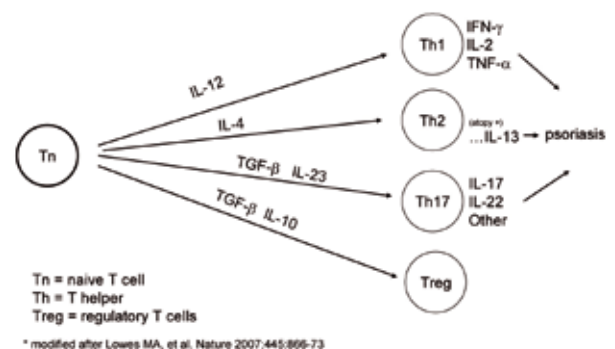


Figure 2. T cell differentiation in psoriasis.

Ustekinumab was assessed in psoriasis patients in a phase III, randomized, double-blind, placebo-controlled 76-week clinical trial (Phoenix 1) (9). Adult patients (n=766) with moderate to severe plaque psoriasis were randomized and treated for 76 weeks with ustekinumab 45 mg or 90 mg (at week 0, 4 and every 12 weeks) or with placebo (for the first 12 weeks, and after week 40, between w12 and w40, they received ustekinumab 45 or 90 mg every 12 weeks). The Psoriasis Area and Severity Index (PASI) 75 was achieved at week 12 by 171 (67.1%) patients receiving ustekinumab 45 mg, 170 (66.4%) patients receiving ustekinumab 90 mg, and eight (3.1%) patients receiving placebo. At week 40, long-term response was achieved by 150 patients in the 45-mg group and 172 patients in the 90-mg group. Serious adverse events occurred in six (1.2%) of 510 patients receiving ustekinumab and in two (0.8%) of 255 receiving placebo in this phase. The pattern of adverse events was the same in the placebo crossover and randomized withdrawal phases (placebo-controlled phase).

Another placebo-controlled, double blind study (Phoenix 2) (10) was performed in a series of 1230 patients with moderate to severe psoriasis patients receiving ustekinumab 45 mg or 90 mg at week 0, 4 and every 12 weeks for 52 weeks, or placebo only at week 0 and 4, then randomized to ustekinumab 45 or 90 mg (10). PASI 75 at week 12 was achieved by 273 (66.7%) patients receiving 45 mg, 311 (75.7%) patients receiving

90 mg, and 15 (3.7%) patients receiving placebo. At week 28, PASI 75 was similar to that recorded in Phoenix 1 study in both groups of patients. Serious adverse events were observed in eight (2.0%) patients in the 45-mg group, five (1.2%) patients in the 90-mg group, and eight (2.0%) patients in the placebo group.

A phase II 12-week, multicenter, randomized, double-blind, placebo-controlled trial using anti-IL12/23 fully humanized monoclonal antibody ABT-784 was performed in a series of 180 patients with moderate to severe chronic plaque psoriasis that were randomized (groups of 30) to receive one of 6 treatments with ABT-874: one 200-mg dose at week 0; 100 mg every other week for 12 weeks; 200 mg weekly for 4 weeks; 200 mg every other week for 12 weeks; 200 mg weekly for 12 weeks; or placebo. PASI 75 at week 12 was achieved in 63% of patients on 200 mg once; 93% of patients on 100 mg every other week; 90% of patients on 200 mg weekly for 4 weeks; 93% of patients on 200 mg every other week for 12 weeks; 90% of patients on 200 mg weekly for 12 weeks; and in 3% of patients on placebo. There were no serious adverse events (11).

It is obvious that nobody currently provide answer to the provocative title-question of this paper. At the same time, the results of clinical trials using anti-IL12/23 were promising in terms of efficacy and safety. Larger series of patients are necessary to offer more information on the safety profile of these new agents, taking into account that IL-12

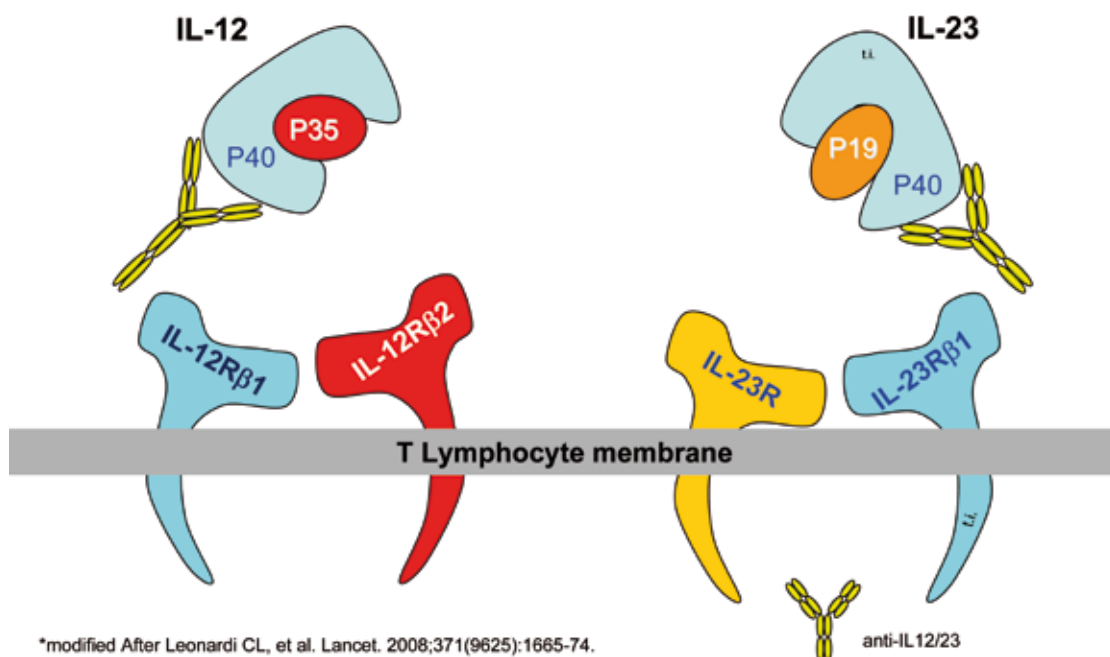


Figure 3. Interleukins 12 and 23 with their p40 subunit: target for anti-IL12/23 biologics.

is an immunoregulatory cytokine with an important role in both innate resistance and antigen-specific adaptive immunity (15,16).

CONCLUSIONS

Anti-IL12/23 ustekinumab and ABT-874 are new therapeutic agents acting on the early steps of the inflammatory cascade in psoriasis. Larger studies are ongoing and will provide more information on the effects, adverse events and precise indications of anti-IL12/23 therapies and their place in the treatment of moderate to severe plaque psoriasis. In the meantime, therapeutic experience acquired to date with the use of anti-TNF biologics in rheumatology, psoriatic arthritis and moderate to severe plaque psoriasis strongly supports TNF-antagonists as important elements of psoriasis therapy today.

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