The New Era of Biological Treatments

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For many decades we considered (and still consider) tumor necrosis factor-alpha (TNFα) to be a leading pro-inflammatory cytokine in the pathogenesis of rheumatoid arthritis (RA) and other immune mediated diseases. This explains why anti-TNF drugs led the revolution of the biologics, changing the entire therapeutic approach in these diseases as well as the prognosis of RA [1]. During the last two decades we became familiar with many anti-TNF therapies, some of which include monoclonal antibodies while others comprise soluble TNF molecules. All these changed the course of RA, ankylosing spondylitis and psoriatic arthritis and were efficient in sparing steroids and altering their side effects and those of many other cytotoxic drugs [2]. Anti-TNF inhibitor therapies are widely used as a first-line biotherapy in patients who failed traditional non-biologic disease-modifying anti-rheumatic drugs (DMARDs). However, about 30% of these patients are usually defined as failures of first-line anti-TNF agents due to inefficacy or adverse events [3]. Later, we became aware of the role of many other pro-inflammatory cytokines such as interleukin-6 (IL-6), interferon-gamma (IFNγ) and others, which, when targeted, improved the course of many autoimmune diseases including RA, vasculitides and systemic lupus erythematosus (SLE). IL-6 is indeed a front cytokine in immune regulation responses and its over-production is involved in many autoimmune diseases. Levels of serum IL-6 were reported to be increased in association with SLE disease activity and the production of relevant autoantibodies. Increased levels of serum IL-6 have also been reported to shift the balance between IL-17-producing T helper (Th) 17 cells and T regulatory cells (Tregs), thus contributing to the development and disease activity of RA [4]. With this in mind, rheumatologists were armed with another member of the biologics – namely, anti-IL-6 (tocilizumab) which became one of the efficacious therapies in RA and autoinflammatory diseases.

Secukinumab, a humanized anti-IL-17 antibody, was found to be a potential treatment in RA, psoriatic arthritis and ankylosing spondylitis

Tocilizumab has been shown to dissociate IL-6 and sIL-6R from their pre-formed complex and suppress the IL-6/IL-6R complex-induced proliferation of human gp130-transfected cells [5]. In one of our studies we reported another mechanism of action, namely, a shift in B cell properties following tocilizumab treatment. These were: the alteration in the activation status (CD69 expression), APC properties (MHCII expression), and the expression of the inhibitory cytokine transforming growth factor-beta (TGFβ) in CD25high B cells, suggesting that the induction/expansion of B regulatory cells may be one of the mechanisms by which tocilizumab possibly produces its beneficial clinical effects [6]. The era of considering immune mediated inflammation as primarily a result of Th1/Th2 misbalance, and as such the over-production of pro-inflammatory cytokines, is over. It is also a simplified explanation to assume that inflammation is the result of a decreased number or function of T regulatory cells. Th17, a distinct subset of CD4+ T cells with IL-17 as their major cytokine, is frequently reported as a front player in the pathogenesis of inflammatory or autoimmune diseases [7]. Cytokines and cytokine receptors, such as the p40 subunit of IL-12/IL-23, are also reported as new players in the field of autoimmunity. The role of Janus tyrosine kinases JAK1 and JAK3 in initiating inflammatory immune responses also contributed to our current understanding of autoimmune diseases [8]. With all this in mind, these cytokines/signaling molecules became reasonable candidates to be targeted for the development of new biological therapies. In this review we will discuss some of the new biologicals, their mechanisms of action, indications, and future place in the arsenal of all therapeutic options in this field.

IL-17 AND THE NEW EMERGING ANTI-IL-17 THERAPIES

T helper 17 cells are the main source of IL-17, IL-21 and IL-22, all of which play a critical role in initiating chronic inflammatory responses and subsequent tissue damage in the skin and joints. Th17 cells co-express IL-22, and its receptor is expressed on epidermal keratinocytes. Both IL-17 and IL-22 cooperatively enhance the production of certain cytokines and chemokines by keratinocytes; thus not surprisingly, they are profoundly involved in the pathogenesis of certain skin disorders such as

psoriasis, atopic dermatitis and drug-induced hypersensitivity. Being a key product of Th17 cells, IL-17 is also produced by neutrophils, mast cells, and Tc17 cells. Each of these cell types is found in psoriatic lesions. IL-17 acts on keratinocytes to increase expression of chemokines such as CXCl1, CXCL3, CXCL6 and others. Over-expression of IL-17A induces systemic endothelial dysfunction, vascular oxidative stress and arterial hypertension, and increases myeloperoxidase (+) CD11b (+) GRI (+) F4/80 (-) inflammatory cells in psoriatic-like skin diseases [9]. The percentage of Th17 cells was found to be increased in the peripheral blood of patients with atopic dermatitis and associated with disease severity. Drug-induced skin reactions constitute another disease in which Th17 cells are involved. Here, both Th17 and IL-22 were also found elevated in patients with these drug-induced hypersensitivity conditions. Th17 and IL-22 are increased in patients with acute generalized exanthematous pustulosis. In this respect, both these cytokines stimulate keratinocytes to produce IL-8, contributing to the accumulation of neutrophils in the skin and emphasizing their role in skin inflammatory diseases [10].

Th17 cells are also involved in the pathogenesis of systemic sclerosis (SSc). The ratio of Th17 in SSc patients was significantly elevated compared to healthy controls, and was positively correlated with disease duration, systemic involvement and the presence of specific autoantibodies such as anti-topoisomerase I and anti-U1 ribonucleoprotein (RNP) antibodies. Other studies showed IL-17 to be increased in patients with SSc in part due to the diminished immune suppressive T regulatory capacity, and their abnormal expression of CTLA4. In a recent study, Th17 cell numbers were elevated in SSc, and FoxP3 (low) CD45 RA (-) T cells produced IL-17, confirming their Th17 potential which was consistent with elevated levels of FoxP3 (+) IL-17 (+) cells in SSc [11]. Increased IL-17 levels and insufficient capacity of Tregs to suppress inflammation was also reported in patients with chronic obstructive lung disease (COPD), especially during acute exacerbations, suggesting a crucial role of IL-17 in favoring pro-inflammatory imbalance in COPD [12]. The involvement of IL-17 in rheumatoid arthritis was shown in an animal model by its contribution to the development of angiogenesis, neovascularization, endothelial cell activation, migration and proliferation. Additionally, IL-17, in concentrations present in the RA joint, induces human lung microvascular endothelial cell migration mediated through the PI3K/AKT1 pathway. The suppression of this pathway markedly reduced IL-17 in RA synovial fluids, supporting the concept of IL-17 as an angiogenic mediator in RA, and thus a potential therapeutic target in RA [13]. Finally, Th17 cells and the increased production of IL-17 were shown to play a critical role in tissue damage of synovial joints of patients with RA. This might establish a vicious cycle culminating in the striking marginal erosions of cartilage and bone in the RA joints and therefore partially abrogating the potential therapeutic benefits related to IL-17 antagonizing therapy [14]. As a result of all the above, the efficacy and safety of various new humanized anti-IL-17 monoclonal antibodies are studied mainly in psoriasis, psoriatic arthritis and rheumatoid arthritis.

ANTI-IL-17 DRUGS AND PSORIASIS

In two different phase II multicenter, randomized, double-blind, placebo-controlled, dose-ranging studies, brodalumab (human monoclonal antibody directed against IL-17RA, the receptor of IL-17A) in one and ixekizumab (humanized anti-IL-17 monoclonal antibody) in the other, were assessed for their beneficial effect in severe chronic plaque-type psoriasis by the Psoriasis Area and Severity Index (PSAI) > 12. In the first study [15] 198 patients were enrolled and received placebo or brodalumab at a dose of 70 mg, 140 mg, 210 mg and 280 mg administered subcutaneously. In the second study [16] 142 patients were enrolled and received subcutaneous injections of ixekizumab (10 mg, 25 mg, 75 mg and 150 mg) vs. placebo. Both studies reported a significant reduction in PASI score at week 12, by at least 75%, when both anti-IL-17 therapies were compared to placebo. A 100% reduction in the PASI score was achieved in significantly more patients when higher doses were given. For difficult-to-treat areas such as the scalp and nails, significant differences were observed with ixekizumab treatment compared to placebo. Although both therapies were considered safe, long-term studies are underway to establish their safety profile. A recent study assessed the long-term efficacy and safety of ixekizumab in maintaining a significant reduction of PASI. Of the 120 psoriatic patients who were given 10, 25, 75, or 150 mg of ixekizumab or placebo, 103 completed 52 weeks or more of treatment and 77% of them achieved PASI 75, leading to the conclusion that anti-IL-17 therapy maintains long-term clinical response for at least one year [17]. Later, two phase III, double-blind, 52 week trials were performed to assess the beneficial outcome of secukinumab in psoriasis. The first was ERASURE (Efficacy of Response and Safety of two fixed Secukinumab Regimens in psoriasis). The second was FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept) using two dosing regimens to determine efficacy in psoriasis. In the ERASURE study 738 patients received secukinumab at dose of 300 mg or 150 mg vs. placebo, while in the FIXTURE study 1306 patients received etanercept at a dose of 50 mg vs. placebo. The proportion of patients who achieved PASI 75 at week 12 was significantly higher with both secukinumab doses than with placebo and etanercept; these results demonstrated that anti-IL-17 therapy was effective for psoriasis in two phase III randomized trials, validating this new therapeutic approach as highly beneficial

UST (Ustekinumab) had a significant beneficial effect on articular and dermatologic symptoms in psoriatic and PsA patients

[18]. Anti-IL-17 agents, namely secukinumab, were shown to be beneficial in patients with psoriatic arthritis and were therefore recently added to a broad-treatment armamentarium. Other anti-IL-17 agents, ixekizumab and brodalumab, have very limited but promising data for the concurrent management of skin and joint psoriasis [19].

ANTI-IL-17 DRUGS IN RHEUMATOID ARTHRITIS

In conjunction with studies using the humanized anti-IL-17A monoclonal antibody (mAb) ixekizumab (LY2439821) and the fully human anti-IL-17A mAb brodalumab (AMG 827), the findings on secukinumab provide evidence for the role of IL-17A in the pathophysiology of many autoimmune diseases and suggest the potential value of these drugs in RA, psoriatic arthritis and ankylosing spondylitis [20]. In a phase I randomized, double-blind, placebo-controlled, proof-of-concept study, LY2439821 (ixekizumab) was assessed in RA patients, mainly evaluating its efficacy, safety and tolerability. The percentages of American College of Rheumatology (ACR) 20, ACR50 and ACR70 responses were higher in ixekizumab-treated patients than in placebo-treated patients at multiple time points. This drug, added to oral DMARDs, improved signs and symptoms of RA, and no strong adverse safety signals were noted [21]. A recent phase II, dose-finding, double-blind, randomized, placebo-controlled study evaluated the one year efficacy and safety of secukinumab in RA. Of 237 randomized patients, 174 (73.4%) completed the study. Patients with improved ACR and 28-joint Disease Activity Score (DAS28) responses at week 16 sustained their responses through week 52. Patients with active RA who failed to respond to DMARDs and other biologics showed improvement after long-term treatment with 150 mg of secukinumab [22]. Anti-IL-17 antibody therapy seems to be highly effective in patients with active RA, and phase III trials are underway to further establish these promising results.

Tofacitinib, an anti-JAK treatment, ameliorates RA activity and synovial damage as well as psoriasis and psoriatic arthropathy

ANTI-IL-12 AND IL-23 ANTIBODIES FOR PSORIATIC ARTHRITIS

Research in psoriatic arthritis has been lagging behind that in rheumatoid arthritis for years and until recently most of the treatment was borrowed from rheumatoid arthritis. Accelerated interest and research in the last decade has revealed new pathways in pathophysiology and hence new treatment for psoriatic arthritis. Among these are the interleukin-12 (IL-12) and interleukin-23 (IL-23) pathways.

Ustekinumab (UST) is a good example of genetics translated into medical practice. In 2007 several genetic studies using genome-wide association scans (GWAS) identified a significant association of psoriasis and psoriatic arthritis (PsA) with single-nucleotide polymorphisms (SNPs) in the *IL12B* gene (which encodes the p40 subunit common to both IL-12 and IL-23) and in the *IL23R* gene [23]. Major increases in risks between the highest and lowest two-locus risk genotype classes (25-fold for *IL12B* and 16-fold for *IL23R*) were found independent of *HLA-Cw6* susceptibility to psoriasis. These findings led to further interest in the role of these cytokines in psoriasis and PsA. UST is a fully human immunoglobulin G1κ (IgG1κ) monoclonal antibody against the common sub-unit p40 of IL-12 and IL-23. IL-12 and IL-23 are essential for the induction and maintenance of the Th1/Th17 immune response, respectively, which is the main cytokine profile of psoriasis. IL-23 activates Th17, which produces IL-17, activating dendritic cells to produce IL-12, hence stimulating Th1 [24,25].

Six large clinical trials (including four phase III trials: PHOENIX 1, PHOENIX 1, ACCEPT and PEARL with a total of 1322 patients) have shown UST to be an excellent drug in the management of cutaneous psoriasis, with a 75% PASI score reached in about 70% of patients and long-term effect up to 36 weeks [26]. Following the encouraging results seen in psoriatic skin disease, three large trials evaluated UST in PsA. In 2009, the first phase II, double-blind, randomized, placebo-controlled and crossover study of UST was published, which showed significant amelioration of articular and dermatologic symptoms in PsA patients [27]. This study comprised 146 patients and demonstrated at week 12 an ACR20 response of 42.1% with UST compared to only 14.3% in the placebo control. Interestingly, only 20% of the patients received methotrexate (MTX). These results were validated in a double-blind, placebo-controlled phase III trial, PSUMMIT 1, which included 615 patients naïve to biologic drugs [28]. The ACR 20% response was similar to that of the earlier study, 42% vs. 22% in the placebo group; and the ACR 50% was 25% compared to only 9% in the placebo group. In this study half the patients were taking MTX, but in the sub-analysis MTX did not improve the response rate. An interesting finding of this study was the impressive response of enthesitis (about 80%) and dactylitis (100% improvement) to UST. Recently published were the results of a third randomized control phase III trial, PSUMMIT II [29]. This study evaluated 132 anti-TNFα naïve patients as well as 180 who had failed or had an adverse reaction to anti-TNF agents. The ACR 20% in patients who had failed anti-TNF agents in the past (44%) was only slightly lower than in naïve patients (37%). The study's results validated the beneficial effect of UST on dactylitis and enthesitis, with median percent improvements of 95.0% and 50.0% in dactylitis and enthesitis scores among UST-treated patients, respectively. Another important finding was the evidence of inhibition of radiographic progression of joint damage in patients with active PsA as evaluated by a PsA-modified radiographic score.

SAFETY

In multiple trials that evaluated thousands of patients, UST was found to be a safe drug with an infection rate comparable to that in the placebo group. In 2012, a 4 year safety analysis by Reich and colleagues [30] of 3117 patients who received at least one dose of UST during the phase II study, PHOENIX I or II or the ACCEPT study, demonstrated consistent safety up to 4 years [30]. Interestingly, there was no indication of an increasing trend in the incidence of serious infections, non-metastatic skin cancer (NMSC), malignancies other than NMSC, and major adverse cardiovascular events (MACEs) compared with the expected levels based on population-matched rates. They specifically studied the cardiovascular events in placebo-controlled groups and concluded that there was no increased risk of myocardial infarction or stroke in UST-treated patients compared with the general population as well as non-UST-treated psoriasis patients. No cases of active tuberculosis have been reported with UST, yet prophylactic therapy for latent tuberculosis is advised. Of note is one case of reversible posterior leukoencephalopathy syndrome (RPLS) that was reported in a patient after approximately 2 years of treatment.

In conclusion, UST has shown good results in terms of safety and efficacy in PsA patients. Especially in patients in whom TNFα inhibitors fail primarily or secondarily, UST should be considered. Long-term safety is yet to be studied more thoroughly. Following proper guidelines for choosing patients and screening them is essential for a good outcome.

JAK INHIBITOR TREATMENT IN RA AND PSORIASIS

The issue of targeting intracellular signaling pathways represents an emerging field in inhibiting the pro-inflammatory effects of cytokines, and a promising alternative or additive to the current DMARD and biologic treatment option in immune mediated diseases. These drugs are easy to synthesize and are available for oral administration. Several protein kinase inhibitor subgroup proteins have been tested in randomized clinical trials; among them are inhibitors of mitogen-activated protein kinase/p-38, spleen tyrosine kinase, c-Kit-activated kinases, and Janus kinase (JAK). The JAK family, JAK1, JAK 2, JAK 3 and Tyk2, are non-receptor tyrosine kinases with a variety of intercellular domains. JAK1 and JAK2 play a role in growth, neurodevelopment, hematopoiesis and host defense, while JAK3 and Tyk2 are involved in immune responses. The main functions of the activated JAK family members include cytokine signaling, pro-inflammatory cytokine production, and immune cell activation [31]. Binding of cytokines to heterodimers of JAK receptors (JAK1/JAK3, JAK1/JAK2, JAK1/Tyk2, JAK2/JAK2) induces phosphorylation of tyrosine residues on the cytokine receptor, and subsequent activation of various signal transcription (STAT) molecules. This promotes JAK activity and further recruitment of cytokines. JAK3 binds to the common IL-2Rγ chain of the type I cytokine receptor family (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21), which is crucial for T cell activation. On the other hand, JAK1 binds with γ-chain cytokines (IL-6, IL-10, IL-13, IL-22, granulocyte colony-stimulating face, interferons). Thus, inhibition of JAKs is responsible for decreased pro-inflammatory cytokines signaling via inhibition of cytokine production, such as IL-2, IL-4 and IL-6, decreased receptor activator of nuclear factor-κB ligand production, and decreased production of TNF-stimulated fibroblast-like synoviocytes. So it seems that JAKs and STATs are pivotal players in several immunologic pathways, including regulation of proliferation, survival and differentiation. Other molecules, such as interferons, interleukins, colony-stimulating factors, and other cytokines share the same pathway of signal transduction [32,33].

Several studies, conducted on both animal models and human inflammatory cells, have revealed enhanced JAK-STAT pathway gene expression, supporting the hypothesis that this pathway is fundamental in inflammatory response regulation. This signal transduction pathway was found to be altered in inflammatory arthritides due to changes in STAT expression and function. Therefore, the ability to modulate the JAK-STAT pathway makes it a potential target for alternative therapeutic approaches to pro-inflammatory cytokine activity (i.e., TNFα, IL-1 and IL-6), as observed in RA [34,35].

Tofacitinib is a pan-JAK inhibitor with potent inhibition of JAK3 and JAK1 and to a minor degree JAK2. The net effect of tofacitinib is decreased body and synovial inflammation and structural joint damage in RA patients by limiting T cell and other leukocyte recruitment. Other immune cells involved in RA pathogenesis express JAKs and may also be affected by tofacitinib inhibition. This drug is currently used as a commercial formulation (Xeljanz®, Pfizer, Inc., New York, USA) and is supplied for oral administration as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate). Tofacitinib binds to the active site of TyK2 and blocks the STAT activity, thereby influencing gene expression cellular processes, including hematopoiesis and immune responses. In clinical studies it is notable that treatment with this drug caused an early, dose-dependent depletion of T and B lymphocytes, which returned to normal 1 month after discontinuation of the drug. It was also noted that tofacitinib treatment in RA patients causes a decrease in C-reactive protein (CRP), which persists even after 2 weeks of drug discontinuation. The pharmacokinetics of this drug demonstrates that the peak plasma concentration is reached between 60 minutes and 1 hour after drug administration; since the drug's half-life is a 3 hour range at a therapeutic dose it is administered twice daily. The metabolic clearance of tofacitinib is mainly hepatic (70%) and renal (30%).

Several phase II (A and B dose-ranging) trials, lasting from 6 to 24 weeks, were conducted to test tofacitinb (CP-690,550) in RA patients. All these studies demonstrated an overall sig-

nificant improvement in the ACR20 score as early as week 2 of treatment, and sustained at least until week 24, the end of the study. Significant improvements were noticed at the end of the study, at week 24, for the ACR20, ACR50, and ACR70 responses, as well as for the Health Assessment Questionnaire Disability Index (HAQ-DI) scores and the three-variable DAS assessed in 28 joints using the CRP level (DAS28-CRP) permanently < 2.6. In another phase IIB trial, tofacitinib or adalimumab monotherapy versus placebo was tested in patients with active RA who inadequately responded to DMARDs. In this 24 week, double-blind, phase IIB study, RA patients (n=384) were randomized to receive placebo, tofacitinib at several doses administered orally twice daily, or 40 mg of adalimumab injected subcutaneously every 2 weeks (a total of six injections), followed by oral tofacitinib at 5 mg twice a day for 12 weeks. Tofacitinib was found to lead to superior treatment effects compared to adalimumab, as demonstrated by the primary endpoint (ACR20 response at week 12). The most common treatment-related adverse events (AEs) observed in > 10% of patients receiving tofacitinib were diarrhea, upper respiratory tract infection, and headache. Serious AEs were reported in 21 patients (4.1%). Some patients exhibited an increase in transaminase, cholesterol, and serum creatinine levels (which occurred parallel to a decrease in neutrophil and hemoglobin levels) [36-38].

A recent study was conducted in patients with psoriasis. The effectiveness and safety of tofacitinib was tested in a phase IIB, randomized, double-blind, placebo-controlled study, where three tofacitinib dosage regimens and placebo were compared in patients with moderate-to-severe chronic plaque psoriasis. Treatment with tofacitinib resulted in significant dose-dependent improvements in life quality and disease activity versus placebo from week 2 onwards. At week 12, the least-squares mean change from baseline for the Dermatology Life Quality Index, Itch Severity Score, and Short Form-36 questionnaire version 2 were significantly greater for all active drug arms versus placebo ($P < 0.05$). At week 12, the end of the clinical trial, the Patient Global Assessment of psoriasis versus placebo showed a significantly greater impact on quality of life in all dose groups [39].

The results of a large phase III cohort of moderate-to-severe RA patients with an inadequate response to TNF inhibitors were recently reported. These patients received treatment twice a day with two different doses of either tofacitinib or placebo. At 3 months, patients given placebo advanced to tofacitinib, according to the study interim results. At that time, ACR20 response rates were above 42% ($P = 0.0024$) for tofacitinib vs. 24.4% for placebo. Improvements from baseline in HAQ-DI scores were -0.43 ($P < 0.0001$) for the 5 mg twice a day tofacitinib vs. -0.18 for placebo; DAS28 < 2.6 rates were 6.7% ($P = 0.0496$) for tofacitinib 5 mg twice a day vs. 1.7% for placebo. The safety profile of the AEs was consistent with previous phase II and phase III studies. The most common AEs observed in these patients were diarrhea (4.9%), nasopharyngitis (4.1%), headache (4.1%) and urinary tract infections (3.0%) across the different dosage tofacitinib groups [40]. Tofacitinib could, therefore, provide an effective treatment option for patients with an inadequate response to TNF inhibitors or MTX therapy. The above therapies will be the subject of many future clinical studies in order to establish their place in the new era of therapies for the above discussed immune mediated diseases.

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