New Approaches in Tumor Necrosis Factor Antagonism for the Treatment of Psoriatic Arthritis: Certolizumab Pegol

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ABSTRACT. The pathogenesis of psoriatic arthritis (PsA) is still under discussion but great advances have been made in the last 2 decades that confirm the central role of tumor necrosis factor-α (TNF-α) in its inflammatory milieu. New therapeutic approaches have been proposed, and new molecules with anti-TNF-α activity have been chemically altered to improve their pharmacological properties. Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF that has been shown clinically to be effective in the treatment of rheumatoid arthritis (RA), skin psoriasis, and PsA. This article summarizes available data on its clinical efficacy and safety profile in the treatment of patients with PsA. (J Rheumatol Suppl. 2015 Nov;93:70–2; doi:10.3899/jrheum.150641)

Key Indexing Terms:
PSORIATIC ARTHRITIS THERAPY CERTOLIZUMAB PEGOL

Psoriatic arthritis (PsA) is a chronic and systemic inflammatory disease that affects both peripheral and axial joints, as well as the skin. According to joint involvement, Moll and Wright[1] classified PsA in the following clinical subsets: polyarticular, oligoarticular, distal, mutilans, and axial. Other clinical manifestations include enthesitis, dactylitis, and uveitis, features that are common in the spectrum of the spondyloarthropathies[2]. Although PsA pathogenesis is complex and controversial, there is agreement that an important role is played by individual genetic background[3,4,5] together with environmental triggers interfering with the innate and acquired immune system. Several cell types[6,7] contribute to the inflammatory milieu, giving rise to the cascade of mediators, which can lead to joint erosion and new bone formation. In this context, recent evidence has supported a primary role for a T cell subset characterized by production of interleukin 17 and therefore named Th17[8].

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Approach to Treatment

International and national guidelines[9,10] for the treatment of PsA suggest starting with nonsteroidal antiinflammatory drugs or steroid joint injections, rapidly followed by disease-modifying antirheumatic agents (DMARD) such as methotrexate, sulfasalazine, leflunomide, and cyclosporine. In patients with inadequate response to traditional DMARD or in patients with axial disease, anti-tumor necrosis factor-α (TNF-α) agents are recommended to control signs and symptoms[11,12]. To avoid joint damage, it is also strongly recommended not to delay the switch to biologic drugs if traditional DMARD fail to control disease activity[9,10]. Recently, apart from classical TNF-α antagonists, new biologic and synthetic drugs with different mechanisms of action or with different structural features have been developed. Ustekinumab[13] and apremilast[14] are among the first ones while certolizumab pegol (CZP) is an example of new technology applied to antibody development in TNF-α antagonism[15].

Development of new therapeutic agents is oriented to find new targets in the pathogenic mechanisms of disease, or to improve the pharmacological properties of the class of effective drugs already in the market. Anti-TNF-α drugs, which antagonize the key inflammatory mediator of PsA and psoriasis (PsO), have been successfully used for the treatment of these diseases for many years; TNF-α therefore represents a referenced target to work on. The majority of biologic drugs are antibodies, or part of antibodies or proteins, all characterized by peculiar pharmacologic properties, such as blood half-life or immunogenicity, which have been deeply investigated by researchers. Structural alterations and molecule conjugations have been done to improve the therapeutic

performance of biologic drugs. Noteworthy among these attempts is the binding of polyethylene glycol (PEG) to biologic molecules, such as parts of antibodies, which has been proven to be successful in improving the pharmacodynamic properties of the final product[16]. PEGylation is the process of covalent binding of PEG to a vast category of substances to alter their physical properties. The large PEG groups alter the solubility in water or biologic fluids (such as serum or synovial fluid), thermal stability and antigenicity, and therefore the possibility to induce antibodies against the drug. Further, it increases the *in vivo* half-life of the drug and inhibits clearance and degradation[17] by means of the increase in the hydrodynamic volume of the compound, which is therefore less excreted by the renal filter because of reduced permeability. PEGylation has been recently implemented in anti-TNF-α antibody technology and applied initially to the treatment of RA and then to spondyloarthropathies.

Certolizumab: Clinical Data

CZP is a PEGylated Fc-free anti-TNF that has been shown to be clinically effective in the treatment of RA[15], and further, effective in the treatment of PsO during a phase II trial[18]. Following satisfactory results obtained in RA and PsO, CZP has been tested in PsA in the RAPID-PsA trial[16], a randomized double-blind placebo-controlled trial, with 2 different dose regimens (200 mg Q2W and 400 mg Q4W doses CZP). CZP was effective in improving the signs and symptoms of PsA; the primary clinical endpoint of the RAPID-PsA study was represented by American College of Rheumatology 20% improvement (ACR20), and differences were observed as early as Week 1, probably because of the CZP loading dose in the first 3 injections (0, 2, and 4 weeks). A statistically significant difference in ACR20 was also observed at Week 12 and maintained up to Week 24. Relevant improvements were also observed for ACR50 and ACR70. Followup data, recently presented during the American College of Rheumatology annual meeting in Boston, revealed sustained efficacy with similar response results at 2 years[19]. Statistically significant improvements were also detected in patient-reported outcomes such as physical function, measured as a reduction in Health Assessment Questionnaire Disability Index scores, in the CZP groups compared to placebo. CZP was also shown to improve dactylitis and enthesitis scores, and achieve fast improvements in skin dermatitis, measured by the Psoriasis Area Severity Index response. Improvements in nail disease were also observed at 6 months. Although it is difficult to compare data from different studies, the improvements in signs and symptoms of PsA with CZP were similar to other phase III TNF-α inhibitor studies in PsA[20]. Although the RAPID-PsA trial was not designed to test equivalence between the 2 CZP dosing schedules, nevertheless, kinetics curves over time did not show substantial differences in the principal outcomes between the 200 mg Q2W and 400 mg Q4W dosing regimens, suggesting dose flexibility. The safety profile of CZP in PsA has shown a similar rate of severe infections compared to that reported in patients with RA treated with CZP. An increased incidence of liver enzyme elevation, generally observed in patients in combined traditional DMARD regimens, has been reported. Two deaths were also reported in the active drug arm of the trial but were considered unrelated to the trial medication by the investigators.

Traditional DMARD used in the treatment of patients with RA have shown limited efficacy in patients with PsA; on the other hand, randomized controlled trials and postmarketing experience with TNF inhibitors have demonstrated the benefit of this class of treatment in PsA[20], changing prognosis and quality of life of patients.

It is important to underline that new players have recently been emerging in the therapeutic scenario for PsA. Among them, ustekinumab (an interleukin 12/23 inhibitor)[13] and apremilast (a phosphodiesterase 4 inhibitor)[14] are the most promising, and they control signs and symptoms of PsA by targeting different steps in the inflammatory pathway. The availability of drugs with different mechanisms of action is particularly important, not only as first-line treatment but also for all those patients who do not respond to anti-TNF-α treatment and therefore appear to have a disease driven by different pathways.

The pathogenesis of PsA is still controversial, but great advances have been done in the last 2 decades. New therapeutic approaches have been proposed, and new molecules with anti-TNF-α activity have been chemically altered to improve the pharmacological properties. These recent advances in biotechnology have created new and promising tools for PsA treatment, providing more options and hope for patients with PsA.

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