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Tumor necrosis factor inhibitors in psoriatic arthritis.

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ABSTRACT

*Introduction***:** Psoriatic arthritis (PsA) is a chronic inflammatory disease that can result in significant disability. With the emergence of tumor necrosis factor inhibitors (TNFi), therapeutic outcomes in PsA have improved substantially. The clinical efficacy and the inhibition of radiographic progression demonstrated by TNFi have transformed the management of PsA. However, there is still an unmet need for a subset of patients who do not respond adequately to TNFi.

Areas Covered: This review provides an overview of the pharmacokinetics of TNFi, the efficacy of TNFi in PsA, and the role of immunogenicity of TNFi in the treatment of PsA. In addition, we address the use of TNFi in the setting of other medications utilized in the treatment of PsA and the potential future role of biosimilars.

Expert Commentary: Monoclonal antibodies exhibit complex and widely variable pharmacokinetics. The study of factors that can affect the pharmacokinetics, such as immunogenicity, is valuable to further define and understand the use of TNFi in PsA, especially in the subset of patients who do not respond adequately to these agents or lose effectiveness over time.

1. Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease that affects the joints, periarticular structures, skin, and nails. The disease can result in permanent joint damage and disability. The prevalence of PsA ranges from 0.06% to 0.25% in developed countries such as the US, UK, and Western Europe. It is common among patients with psoriasis with a prevalence ranging from 6-41% [1]. Treatment of PsA has evolved substantially since the 1990s with introduction of the tumor necrosis factor inhibitors (TNFi). This review will focus on the pharmacology and clinical efficacy of the TNFi in PsA.

2. Psoriatic Arthritis

2.1 Clinical Manifestations

PsA is a heterogeneous condition encompassing a wide range of clinical manifestations that include the key domains of peripheral and axial arthritis, inflammation at tendon/ligament insertion sites (enthesitis), diffuse swelling of an entire finger or toe (dactylitis), nail disease, and psoriasis [2]. The incidence and prevalence of cardiovascular disease and diabetes is increased in PsA [3]. Inflammatory bowel disease and ophthalmic disease, particularly uveitis, are considered extra-articular manifestations of the disease [3-4].

2.2 Risk Factors

Although PsA can occur prior to developing psoriasis, psoriasis usually precedes PsA in the vast majority of patients by approximately 10 years [5-6]. Obesity has been associated with an increased risk of developing PsA not only in patients with psoriasis, but also among patients in the general population [7-8]. Nail disease has been suggested as a potential risk factor for PsA but may also be just an early feature of the disease [1]. Intergluteal/perianal psoriasis, and scalp lesions in psoriasis patients may be associated with a greater likelihood of developing PsA [9].

Other potential associations include a family history of PsA and severe psoriatic dermatoses [10-11].

2.3. Importance of Early Diagnosis

Early diagnosis of PsA is crucial for prevention of disease progression [12] and may also influence development of comorbidities. Early PsA has been defined as within one to two years of the onset of symptoms [13]. Erosions and worse long term physical outcomes have been demonstrated with even a six-month delay in diagnosis [14-17]. Unlike conventional synthetic disease modifying antirheumatic drugs (csDMARDs), TNFi have been demonstrated to prevent or slow radiographic progression of PsA. Early institution of therapy within 6 months of disease initiation results in improved response to therapy and improved long term outcomes [12, 18].

2.4. Treatment

The most widely used consensus treatment recommendations are The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the European League Against Rheumatism (EULAR) recommendations (Figure 1 & 2). Overarching principles of therapy are similar, and include shared decision making with the patient, controlling symptoms and preventing damage, improving quality of life, minimizing or avoiding complications, and assessing comorbidities. A central feature in the treatment of PsA is considering all the domains involved when deciding on a treatment regimen. The GRAPPA and EULAR recommendations favor a "step-up" approach for the treatment of PsA [4,19]. NSAIDS and intra-articular corticosteroids may be effective in reducing pain from inflammation. Traditional oral therapies such as methotrexate (MTX), leflunomide (LEF), and sulfasalazine (SSZ) can decrease inflammation and improve symptoms. Both NSAIDS and csDMARDs are commonly used in PsA, but neither treat all domains of the disease. Other than the TICOPA study, a treat to target

study in PsA [20], there is little data confirming the efficacy of MTX in PsA [21-23]. However, csDMARDS, particularly MTX, continue to be a mainstay of treatment even though they have not been shown to clearly inhibit radiographic progression and there is a paucity of efficacy data. MTX remains the most commonly used therapy for PsA and has good retention rates (e.g, 2-year retention rates of 65%, Lie et al. in 2010 [24]). The GRAPPA recommendations do not specifically delineate MTX as the csDMARD of choice or TNFi as the first biologic DMARD (bDMARD) of choice [4]. TNFi are the first line bDMARD of choice in the EULAR recommendations on the basis of clinical data and evidence of efficacy and long-term safety data that is available compared to other biologic agents, such as the IL-17A inhibitor, secukinumab, and the IL-12/23 inhibitor, ustekinumab [19]. Furthermore, the TNFi have been shown to inhibit progressive joint destruction and are an effective treatment for all domains of the disease [25]. As there is a paucity of data on axial disease in PsA, recommendations are derived from data for axial spondyloarthritis [26-30]. Both organizations recommend bDMARDs after NSAID failure for axial disease and enthesitis as csDMARDs are not efficacious in these two disease domains [4,19]. A distinction between the two sets of recommendations is that GRAPPA recommendations allow for an "expedited therapeutic route" in which csDMARDs are bypassed and a bDMARD may be initiated early. This recommendation is based on a) the efficacy of bDMARDS and relatively little data for traditional oral agents for long term prevention of progression and b) the relative lack of efficacy of oral agents for enthesitis, both particularly in the patient with poor prognostic factors (e.g., elevated C-reactive protein or high joint counts) [4].

2.4.1 Defining Treatment Response

The primary outcome used in PsA randomized controlled trials (RCTs) is the American College

of Rheumatology (ACR)-20% improvement criteria. Patients must achieve at least a 20% improvement in the tender and swollen joint counts and at least three of the five remaining outcome measures: Health Assessment Questionnaire-Disability Index, Patient pain assessment, Patient global assessment, Physician global assessment, C-reactive protein. Psoriasis severity is measured in RCTs using the Psoriasis Area and Severity Index (PASI) score. The PASI75 is an improvement of at least 75% in the PASI score [31]. PASI75 (or even PASI90) is generally a secondary outcome in RCTs examining therapies for PsA. While ACR20 and PASI are the most commonly used outcome measures in trials, these measures are not often used in clinical practice. Instead a variety of outcome measures are used including joint counts, enthesitis measures, dactylitis assessment, psoriasis severity, and patient reported outcomes [6, 32].

3. Tumor Necrosis Factor

In 1975, TNF was recognized as an endotoxin-induced glycoprotein that caused hemorrhagic necrosis of transplanted sarcomas in mice [33]. Since then, it has been associated with a wide range of biologic conditions and has been identified as an important pro-inflammatory cytokine [34]. Overexpression of TNF has been implicated in the pathogenesis of a wide variety of diseases, such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and PsA [35-36]. TNF is a pleotropic cytokine that is produced by cells such as activated macrophages, T lymphocytes, monocytes, neutrophils, mast cells, endothelial cells, fibroblasts, and osteoclasts. It is a key driver of many inflammatory activities in the body and also contributes to cell proliferation, apoptosis, and angiogenesis [35, 37]. Transmembrane TNF (tmTNF), a 26 kDa protein, is cleaved by a metalloproteinase, TNF-alpha-converting enzyme (TACE), and is ultimately released as a soluble cytokine, sTNF (17kDa) [34, 38-40]. sTNF and tmTNF can then bind to TNF receptor 1 (TNFR1, p55) or TNF receptor 2 (TNFR2, p75) and exert biological

effects on various cell types [34, 38]. TNFR1 and TNFR2 use different signaling mechanisms; they have differing affinities to ligands and distinct cellular expression profiles [38]. These differences may contribute to varied biological responses [34, 41].

4. Role of TNF in the Pathogenesis of PsA (Figure 3)

While genetic and environmental factors may play a role in the development of PsA, the immune response to such triggers is what sustains the disease. Inflammation in PsA is thought to be driven both by the Th1 and Th17 pathways. In both pathways, TNF superfamily proteins are important for sustaining inflammation [42]. When the inciting antigen is presented to the initial T-cell, unregulated IL-12 causes differentiation and propagation of Th1 cells and contributes to the release of pro-inflammatory cytokines, including TNF [43]. Conversely, IL-23 is thought to play a key role in the pathogenesis of PsA by triggering Th17 cell differentiation [44]. This leads to production of IL-22 and IL-17. IL-17 leads to upregulation of TNF [45]. TNF, along with several other cytokines, induces expression of receptor activator of nuclear factor-κB ligand (RANK-L), a member of the TNF superfamily, promoting osteoclastogenesis and eventually erosion formation [46]. TNF also induces expression of Dickkopf-related protein 1 (Dkk-1) by synovial fibroblasts, inhibiting osteoblastogenesis, further promoting erosions [46].

5. TNF Inhibitors

Etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab are the TNFi that have been approved for PsA in the US and UK. Etanercept was the first FDA approved TNFi for the treatment of PsA in January 2002.

5.1 Structure and Mechanism of Action of TNFi

TNFi are monoclonal antibody therapeutics directed at TNF. IgG monoclonal antibodies are

large proteins that possess hydrophilic properties [48]. They consist of two unique heavy chains and two unique light chains each of which has constant and variable domains [48]. The heavy and light chains are linked by disulfide bonds and connected by disulfide bonds at the hinge region to a fragment crystallizable (Fc) region [49]. The fragment antigen-binding region (Fab) is the antigen-binding portion and the Fc region is the portion which takes part in Fc mediated actions, such as complement-dependent cytotoxicity and antibody-dependent cell mediated cytotoxicity [50]. The Fc portion also binds to the neonatal Fc receptor (FcRn), which is integral in protecting the antibody from intracellular catabolism [49, 51]. The hypervariable region at the top of the variable domain is where binding to the target antigen occurs [48-49].

With the exception of certolizumab and etanercept, the remaining three TNFi are full-length bivalent monoclonal antibodies (mAB) [38] (Figure 4). Certolizumab is a humanized (exogenic hypervariable regions) IgG1 monoclonal antibody with a Fab^1 fragment [38, 48]. The hinge region is modified and is linked to polyethylene glycol allowing for better solubility, half-life, bioavailability, and decreased immunogenicity. It has an affinity for both sTNF and tmTNF [52]. Unlike the other TNFi, certolizumab does not have an Fc portion and therefore does not take part in Fc mediated actions [50]. In contrast to the other TNFi, etanercept is a genetically engineered soluble fusion protein that is composed of two extracellular portions of the p75 TNF receptor linked to the Fc portion of human IgG1 [38]. It binds to both sTNF and tmTNF at the receptor binding site, preventing the binding of TNF with the p75 receptor [38, 53]. The short half-life of entanercept may in part be due to a difference in the conformation of the Fc region [38]. In addition, etanercept is the only TNFi of the five that also binds members of the lymphotoxin (LT) family (also members of the TNF superfamily), specifically LTα3 and

LTα2β1 [38]. Infliximab is unique in that it is a chimeric IgG1k mouse and human monoclonal antibody that consists of human constant regions of IgG1k and murine variable regions [38, 54]. It binds to both sTNF and tmTNF with high affinity via the E-F loop, blocking the ability of TNF to bind to its receptors [55]. Adalimumab is a recombinant human IgG1 antibody. It occupies the TNF receptor-binding site of both sTNF and tmTNF with high affinity, preventing the binding of TNF to its receptors [54-55]. Like adalimumab, golimumab is a human immunoglobulin IgG1 monoclonal antibody that binds to both sTNF and tmTNF [38, 56]. (Table 1)

5.2 General Pharmacokinetic Properties of TNFi

5.2.1 Absorption

As large protein molecules with poor membrane permeability, TNFi are administered parenterally. The oral bioavailability is very low as they are denatured in the acidic environment of the stomach or they undergo a rapid proteolytic cleavage in the GI tract [49, 57]. It is hypothesized that monoclonal antibodies are absorbed via the lymphatic system by convection and diffusion across blood vessels [49, 51]. Absorption can take anywhere from about one to eight days [58]. Most of the TNFi are administered subcutaneously (infliximab is intravenous only and golimumab can be given IV or subcutaneously), which can cause variability among patients in regards to the amount of drug absorbed [59].

5.2.2 Distribution

Given their large weight and hydrophilic nature, monoclonal antibodies usually have a small volume of distribution [49]. The molecules usually reside in the vascular and interstitial spaces and are distributed via paracellular movement by convection and via transcellular movement by endocytosis (phagocytosis, receptor-mediated endocytosis, or fluid-phase pinocytosis) [49, 51].

Convective transport is driven by the blood-tissue hydrostatic pressure gradient. Osmotic pressure gradients and the characteristics of the paracellular pores also affect convective transport [58].

5.2.3 Metabolism and Excretion

Since monoclonal antibodies are large molecules, they are not predominantly renally excreted. The PEG portion of certolizumab decreases its renal excretion secondary to increasing the size of the molecule [52]. Very little is also excreted in bile [49, 51]. These molecules undergo catabolic metabolism via Fc-receptor mediated elimination and target mediated elimination (clearance following binding to target) [49]. The Fc portion is also thought to contribute to the long half-life of most of these monoclonal antibodies since it interacts with the FcRn, which has a mechanism that protects these molecules from systemic elimination [60]. **(**Table 2**)**

5.3 Pharmacokinetics of TNFi

TNFi differ in their pharmacokinetic (PK) properties. Underlying disease type or severity, body weight, immunogenicity, and the concomitant use of other medications such as MTX can impact PK parameters. Elimination of TNFi for the treatment of PsA generally follows linear kinetics and volume of distribution is that of the central compartment (~6 L). [48, 61-66]. Table 3 outlines the pharmacokinetics of monoclonal antibodies utilized in rheumatic diseases with an emphasis, when available, on population pharmacokinetic parameters in PsA.

5.3.1 Obesity

Obesity impacts the pharmacokinetics of TNFi. Higher disease activity is seen in obese PsA patients and disease registries suggest obesity is associated with a decreased response to TNFi [78]. PsA patients on TNFi that lost >5% from their baseline weight were found to be significantly more likely to achieve minimal disease activity (MDA) than patients who did not

lose weight [79]. Obesity may affect the pharmacokinetics of TNFi secondary to insufficient dosing, changes in volume of distribution, and increased drug elimination. [48, 78].

5.3.2 Immunogenicity

Immunogenicity, the ability of a substance to cause an immune response [49], can play a role in the varying pharmacokinetics of monoclonal antibodies. The underlying disease, duration of treatment, route of administration, concomitant medications, dose frequency, genetic predisposition, assay methodology, and the type of antibody can all affect the immunogenicity of TNFi [80-82]. Humanization of monoclonal antibodies may help to decrease immunogenicity [48, 51]. Thus, the chimeric structure of infliximab can account for its high immunogenicity potential. A meta-analysis of TNFi immunogenicity in RA, inflammatory bowel disease, and spondyloarthritis (PsA and ankylosing spondylitis) among patients using one of the five TNFi demonstrated infliximab was the most and etanercept the least immunogenic [83]. There is sparse data regarding the extent of immunogenicity of golimumab and certolizumab in PsA. The elimination rate of TNFi is impacted by immunogenicity. Anti-drug antibodies will increase the elimination rate of TNFi [48, 67, 75, 80]. They may form immune complexes with the drug accelerating its clearance [84]. Small studies have demonstrated a correlation between anti-adalimumab antibodies and decreased serum concentration and thus decreased clinical response [85-86]. Another small study demonstrated elevated levels of anti-drug antibodies to adalimumab and infliximab, but not etanercept in PsA patients, which correlated with low therapeutic drug levels and thus decreased drug efficacy [87].

5.3.3 Concomitant use of MTX and Immunogenicity

There is an association between MTX, a widely used therapy in PsA, and the development of anti-drug antibodies. A meta-analysis by Thomas et al showed that MTX can attenuate the

formation of antibodies by 74% overall and antibodies decreased clinical response by 18% overall in SpA (based on 4 studies looking at infliximab, adalimumab, and etanercept [83]. In RCTs of infliximab and golimumab, a greater proportion of patients on TNFi monotherapy were positive for antibodies compared to those taking concomitant MTX [88-89]. However, efficacy of TNFi is not generally impacted by MTX use [88-94]. Interestingly, a post-hoc analysis determined that patients who were taking combination MTX and golimumab had a ten percent greater improvement in nail, dactylitis, and enthesitis scores compared to those not taking MTX [89]. In an observational cohort study of 375 patients with RA or PsA treated with adalimumab, trough concentrations were higher in patients concomitantly taking MTX and lower in patients on adalimumab monotherapy [95].

6. Key Clinical Trials of TNFi in PsA

TNFi in PsA were found to be efficacious with tolerable safety profiles in pivotal phase III trials (Table 4**)**. The most common adverse events include injection site reactions, infusion reactions in infliximab, and infections [6]. All five TNFi demonstrated an inhibition in radiographic progression. In the GO-REVEAL 5-year study, concomitant MTX appeared to reduce radiographic progression [91]. Only the certolizumab trials included patients who were exposed to TNFi previously (19.8% of patients). Interestingly, improvements in ACR 20 response rates at 12, 24, and 96 weeks were observed for both doses regardless of prior TNFi exposure [93, 96].

7. Other Treatment Options for PsA

A number of patients do not respond to TNFi and many more have a loss of response over time. Thus, recognition of the IL-23/IL-17 pathway in the pathogenesis of PsA and molecules that are targeting other cytokines in the pathway have been integral to the development of further medications to treat PsA.

7.1 Apremilast

Apremilast is an oral phosphodiesterase 4 inhibitor (PDE-4i) that is approved for the treatment of PsA. PDE4 mediates the breakdown of cAMP, which regulates inflammatory responses. Thus, PDE4 inhibitors demonstrate anti-inflammatory effects [103]. The clinical efficacy of apremilast in PsA patients who have already been treated with csDMARDS and/or bDMARDS or are on csDMARDS was studied extensively with several pivotal randomized placebo-controlled trials (Table 5). In the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) phase III trials, in PALACE 1, 2, and 3, the primary endpoint, an ACR20 response at week 16, was achieved by significantly more patients taking apremilast 20 mg or 30 mg bid as compared to placebo regardless of prior treatment. bDMARD-naïve patients had higher ACR20 response rates [104-106]. Sustained improvements were seen through week 52 in PALACE 1, 2, and 3. In PALACE 4, patients who were DMARD-naïve were studied over a 52-week period. The primary end point was met for both doses at weeks 16 and 52 [107]. Studies suggested a lack of efficacy of apremilast in axial disease [108-109]. The most common adverse events were diarrhea and nausea [104-107].

7.2 Secukinumab

Secukinumab is a human IgG1 monoclonal antibody that binds to and neutralizes IL-17A. FUTURE 1 and 2 are key phase III, randomized, double-blind, placebo-controlled trials that have demonstrated the efficacy of secukinumab in the key domains of PsA (Table 5) [110-111]. MEASURE 1 and 2 are key phase III, randomized, double-blind, placebo-controlled trials that have demonstrated the efficacy of secukinumab in ankylosing spondylitis and thus should be effective for axial disease in PsA [112]. Additionally, secukinumab has been shown to decrease radiographic progression [110]. Efficacy was noted regardless of concomitant MTX use and

among patients with prior TNF exposure, though the response was lower. Generally, numerically higher ACR responses were noted in the anti-TNF naïve populations. Efficacy was sustained through week 52. Candida infections were more common in secukinumab versus placebo, which may be because IL-17 plays a role in host defense again fungal infections [110-111].

7.3 Ustekinumab

Ustekinumab inhibits IL-12 and IL-23 by binding to the p40 subunit of IL-12 and IL-23. PSUMMIT 1 and PSUMMIT 2 are pivotal phase III, double-blind, placebo-controlled trials that studied ustekinumab in PsA patients and found that there was a significant improvement in joint and skin disease and less radiographic progression compared to placebo (Table 5). In PSUMMIT-1, ACR20 response rates were maintained at week 52 and efficacy was noted regardless of MTX use [113]. In contrast to PSUMMIT-1, in PSUMMIT-2, 58% of patients had been on TNFi previously. Clinical improvement was noted regardless of prior TNF exposure but was again lower (as has been seen in other studies of TNF inadequate responders). Anti-TNF-naive patients appeared to have a higher clinical response than anti-TNF-experienced patients [114]. Phase III, randomized, double-blind, placebo-controlled trials are underway to evaluate the efficacy and safety of ustekinumab in ankylosing spondylitis [117-118]. Ustekinumab has a tolerable safety profile with a low incidence of serious infections and sustained clinical improvement through week 100 [115].

8. Expert Commentary

PsA is a heterogeneous, often debilitating disease that is associated with several comorbidities. Early intervention is vital to prevent disease progression. Although csDMARDS show variable efficacy in PsA [19,22], they have remained key medications in treatment largely in part due to

cost considerations. With the emergence of TNFi, treatment options have vastly expanded for PsA patients. TNFi inhibit radiographic progression and are effective in treating all the domains of PsA [25]. However, some patients do not respond to TNFi or response may wane over time. Thus, the emergence of IL-17A inhibitors, IL-12/23 inhibitors, and small molecule treatments such as apremilast have provided a wider range of therapeutic options for PsA. Although apremilast has the advantage of being an oral medication with a relatively benign side effect profile, its effect on radiographic progression has not been examined. The TNFi agents etanercept, infliximab, adalimumab, and golimumab appear to have ACR20 advantage over newer non-TNFi biologics such as apremilast and ustekinumab, when compared using indirect methods [119]. There are no direct comparative efficacy trials between non-TNFi biologics, however indirect comparisons suggest similar efficacy and safety among available agents [120]. There are also several new medications that are currently being evaluated for the treatment of PsA (Table 6).

Even though there is an emergence of many new therapies in PsA, there is a subset of patients that do not adequately respond to available treatments. Thus, it would be of benefit to further study established therapies in PsA such as TNFi by assessing parameters that affect drug concentrations in this patient population. Given that monoclonal antibodies exhibit complex and widely variable pharmacokinetics, further population PK studies in PsA would be helpful in identifying covariates, such as age, immunogenicity, weight, comorbidities, and concomitant medications, which can influence dose-concentration-effect relationships [80]. Outside of weight based dosing adjustment, individualization of dosing is currently not the standard for monoclonal antibodies in autoimmune disease. A model based approach that links monoclonal exposure with disease state may eventually allow for more individualized dosing based upon

disease phenotype, endotype (biomarker driven) and potentially, though less likely, genotype. In addition to drug concentrations, anti-monoclonal drug antibody levels can play a role on the effect of treatment discontinuation and adverse events such as infusion reactions, which have occurred at a higher incidence in antibody positive patients [81, 88]**.** It can provide insight into whether or not switching to another TNFi or a medication with a different mechanism of action in patients with poor clinical outcomes would be of greater benefit. Thus, having a better understanding of the factors associated with inter-individual variability and the extent of that variability may eventually contribute to potential dosing strategies that can improve clinical outcomes, especially in patients with TNFi failure.

While combination treatment may be common in clinical practice, there is little data regarding its clinical efficacy [4, 19]. However, decreased immunogenicity of TNFi with concomitant MTX may play a role in improving drug survival rates of TNFi [121-122]. In addition, one study noted higher drug levels in a small group of 26 patients on adalimumab combination therapy (with csDMARDS such as LEF, SSZ, or HCQ) compared to patients using adalimumab monotherapy [95]. Prospective, randomized clinical trials of TNFi with various csDMARDs to assess trough antibody drug concentrations, anti-drug antibody levels, the measurement of a clinical response (ACR 20 response), and to further assess the potential long term side effects of combination therapy in PsA would be of value.

9. Five-year View

With further understanding of the pathogenesis of PsA, novel treatment options are emerging. Over the last several years, many effective therapeutic options have been introduced and more are yet to come. Biosimilars, which are products similar to already approved drugs in regard to quality, safety, and efficacy [123], may help to alleviate the economic burden associated with

TNFi. Few studies have evaluated infliximab, etanercept, and adalimumab biosimilars for PsA. These agents have been approved in the United States for PsA based on similar efficacy to the reference product in psoriasis and/or RA [123-124]. Immunogenicity has been the same, and in some cases less than reference products [125]. Switching established patients in ankylosing spondylitis and rheumatoid arthritis from infliximab to the biosimilar product CP-P13 is not associated with a loss of control [126-127]. Extrapolation from other disease states is complicated if alternate dosing regimens are used. RCTs or pragmatic trials specific to PsA may provide beneficial information regarding the efficacy and safety of biosimilars, but with current evidence the use of biosimilars in established or de novo patients appears to reasonable. Similar to their reference products, trials evaluating how the combination of a biosimilar with a csDMARD affects immunogenicity would be of interest. Long-term pharmacoepidemiology studies assessing predictors of response to biosimilars and the effectiveness of switching from the reference product to a biosimilar and vice versa will provide valuable information.

Key Issues

- Psoriatic Arthritis is a chronic, debilitating disease associated with several comorbidities.
- TNFi are a mainstay of treatment in PsA and inhibit radiographic progression.
- Several factors affect the pharmacokinetic properties of TNFi, including underlying disease type or severity, body weight, immunogenicity, and the concomitant use of other medications such as MTX.
- Identifying drug concentrations and anti-monoclonal drug antibody levels may help more quickly identify patients with TNFi failure and may provide insight regarding medication changes.
- Assessing the effect of combination csDMARDS and TNFi on immunogenicity may

contribute to future treatment recommendations.

- While not tested specifically in PsA, biosimilars are expected to have similar efficacy and safety to reference products.

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FIGURES

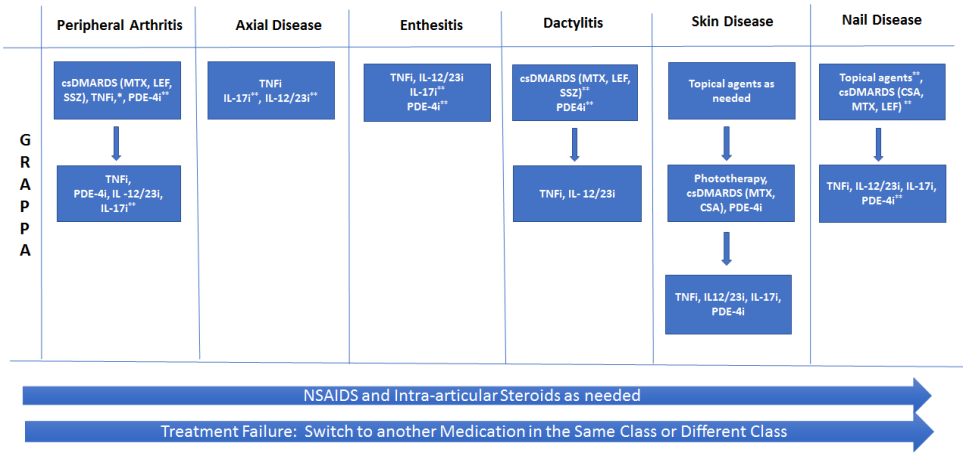

Figure 1. Simplified GRAPPA Treatment Recommendations [4]

*combination csDMARDS and TNFi common in clinical practice

**Conditional recommendations: At the time these recommendations were published, these drugs were not approved or recommendations were based on data from abstracts

csDMARD, conventional synthetic DMARD; CSA, cyclosporin A; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; IL-17i, interleukin-17 inhibitor; IL-12/23i, interleukin-12/23 inhibitor; LEF, leflunomide; MTX, methotrexate; NSAIDS, nonsteroidal anti-inflammatory drugs; PDE-4i, phosphodiesterase 4 inhibitor; SSZ, sulfasalazine; tsDMARD, targeted synthetic DMARD; TNFi, tumor necrosis factor inhibitor

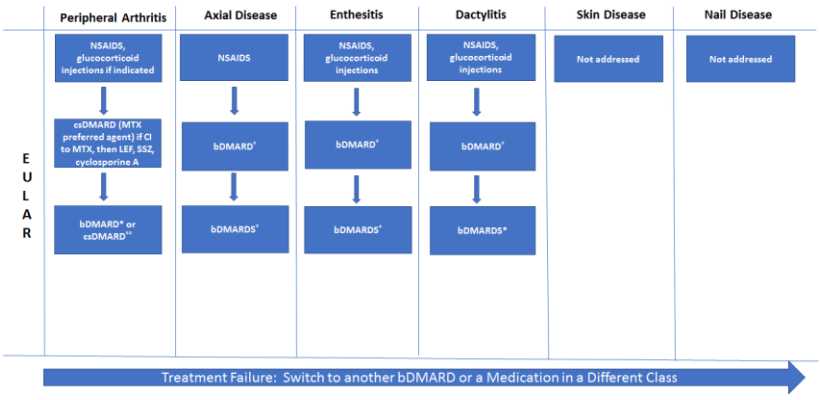

Figure 2. Simplified EULAR Treatment Recommendations [19]

*bDMARD includes TNFi, IL-12/23i, IL-17i. The preference initially is a TNFi, but if contraindicated, can consider one of the others or a PDE-4i.

**no adverse prognostic factors: can try a second csDMARD or combination therapy

bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; CI, contraindicated; EULAR, European League Against Rheumatism; IL-17i, interleukin-17 inhibitor; IL-12/23i, interleukin-12/23 inhibitor; LEF, leflunomide; MTX, methotrexate; NSAIDS, nonsteroidal anti-inflammatory drugs; PDE-4i, phosphodiesterase 4 inhibitor; SSZ, sulfasalazine; tsDMARD, targeted synthetic DMARD; TNFi, tumor necrosis factor inhibitor

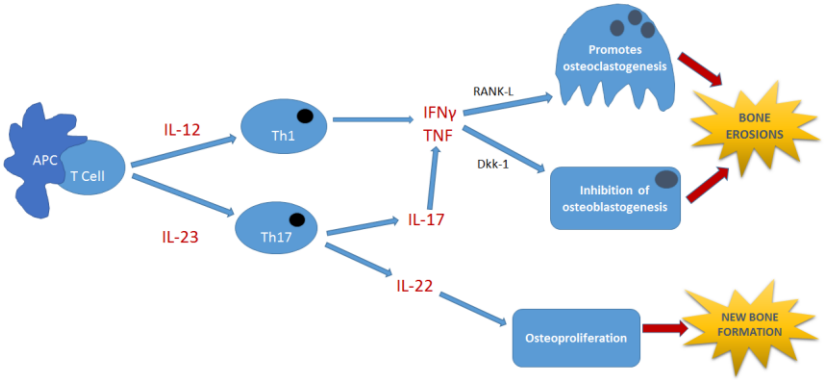

Figure 3. Pathogenesis of Psoriatic Arthritis

The Th1 and Th17 pathways are important pathways involved in the pathogenesis of PsA. TNF, a pro-inflammatory cytokine, is a key player in osteoclastogenesis via RANK-L and in inhibition of osteoblastogenesis via Dkk-1. Both processes eventually lead to bone erosions [46]. In addition, IL-22 is involved in the pathologic formation of new bone (osteoproliferation) [47].

APC, antigen presenting cell; Dkk-1, dickkopf-related protein 1; IFNγ, interferon gamma; IL-12, interleukin-12; IL-17, interleukin-17; IL-22, interleukin-22; IL-23, interleukin-23; RANK-L, receptor activator of nuclear factor-κB ligand; T cell, T lymphocyte; Th1, type 1 T helper cell; Th17, T helper 17 cell; TNF, tumor necrosis factor

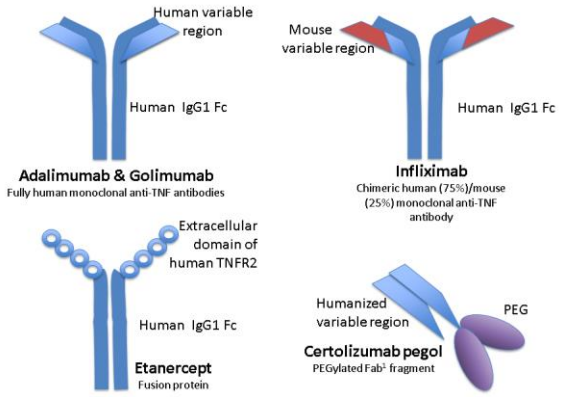

Figure 4. **Simplified structures of TNFi**

Fab, fragment antigen-binding; Fc, fragment crystallizable region; IgG1, immunoglobulin G1; PEG, polyethylene glycol; TNF, tumor necrosis factor; TNFR2, tumor necrosis factor receptor 2

Tables

Table 1. Basic Characteristics of TNFi

TNFi	Structure	Protein Type	Affinity	Fc Portion?
Infliximab	Full length bivalent mAb	Chimeric & Human	sTNF & tmTNF	Yes
Etanercept	Genetically engineered Fc-fusion protein	Recombinant Human	sTNF, tmTNF, LTα3, LTα2β1	Yes
Adalimumab	Full length bivalent mAb	Fully Human	sTNF & tmTNF	Yes
Golimumab	Full length bivalent mAb	Fully Human	sTNF & tmTNF	Yes
Certolizumab Pegol	Monovalent Fab[1] antibody fragment	Humanized	sTNF & tmTNF	No

Fab, fragment antigen-binding; Fc, fragment crystallizable region; LTα3, lymphotoxin alpha 3; LTα2β1, lymphotoxin alpha 2 beta 1; mAb, monoclonal antibody; sTNF, soluble tumor necrosis factor; tmTNF, transmembrane tumor necrosis factor; TNFi, tumor necrosis factor inhibitor

Table 2. General Pharmacokinetic Properties of Monoclonal Antibodies

Absorption	Lymphatic system via convection & diffusion
Distribution	Small volume of distribution, paracellular and transcellular movement
Metabolism and Excretion	Catabolic metabolism

Table 3 Pharmacokinetics of TNFi in Rheumatologic Diseases

	Infliximab	Etanercept [c]	Adalimumab	Golimumab	Certolizumab
Administration	IV	SC	SC	SC	SC
Loading Dose	3-5 mg/kg at 0,2, and 6 wks	-	-	-	400 mg at 0,2, and 4 wks
Maintenance Dosages	3-10 mg/kg every 4-8 wks	50 mg weekly	40 mg eow	50 mg once a month	200 mg eow or 400 mg once a month
Half-life ($t_{1/2}$)	8-10 days [a]	3-5 days	14 days	14 days [d]	14 days
Clearance (L/d)	0.26[b]	1.67	0.269	0.40[d]	0.408
Bioavailability	-	58%	64%	53%	80%
C_{max} μg/ml	192 ± 51[b]	2.4 ± 1.5	4.7 ± 1.6	2.5	43-49 (after loading dose)
References	[38,64,67-70]	[53,65,70,72-73]	[65,70,75]	[61,76]	[65-66]

[a] Population PK in PsA for infliximab: The $t_{1/2}$ life was 15.7 days [71]
[b] based on 5 mg/kg IV in RA patients
[c] PK of etanercept 50 mg once weekly is comparable to 25 mg twice a week SC [74]
[d] Population pharmacokinetics in PsA were characterized using a 1-compartment model. Clearance: 0.68 L/d, $t_{1/2}$ life of golimumab was 12.5 days [77]
eow, every other week; SC, subcutaneous; IV, intravenous; TNFi, tumor necrosis factor inhibitor; wk, week

Table 4. Pivotal Phase III Trials of TNFi in Psoriatic Arthritis

	Reference	Study Size (n)	Doses (vs Placebo)	% Achieving ACR20 Response (tx/placebo) *(primary endpt wk)*	% Achieving PASI75 Response (tx/placebo) *(primary endpt wk)*	Inhibition of Radiographic Progression
Infliximab	IMPACT [97-98]	104	5 mg/kg IV	65.4/9.6 (16)	68/0 (16)	50 wks
	IMPACT 2 [99-100]	200	5 mg/kg IV	58/11 (14)	64/2 (14)	6 months and 1 yr
Etanercept	12 wk study [101]	60	25 mg SC 2x wk	73/13 (12)	26/0 (12)	Not studied
	24 wk study [94,102]	205	25 mg SC 2x wk	59/15 (12)	-	12 months & 2 yrs
Adalimumab	ADEPT [92]	313	40 mg SC eow	58/14 (12)	-	24 wks
Golimumab*	GO-REVEAL [90-91]	405	50 mg/100 mg	51/45/9 (14)	40/58/3 (14)	24 wks & 256 wks
Certolizumab**	RAPID-PsA [93,96]	409	200 mg/400 mg	58/51.9/24.3 (12)	46.7/47.4/14 (12)	96 wks

ACR20, American College of Rheumatology 20% improvement criteria; endpt, endpoint; eow, every other week; IV, intravenous; PASI75, ≥ 75% improvement in Psoriasis Area and Severity Index; SC, subcutaneous; tx, treatment; TNFi, tumor necrosis factor inhibitor; wk, week; yrs, years

*SC dosing every 4 weeks

**200 mg SC every 2 weeks; 400 mg SC every 4 weeks

Table 5. Pivotal Phase III Trials for Other Treatment Options in Psoriatic Arthritis

	Reference	Study Size (n)	Doses (vs Placebo)	% Achieving ACR20 Response (tx/placebo) (wk)	% Achieving PASI75 Response (tx/placebo) (wk)	Less Radiographic Progression
Apremilast	Palace 1 [104]	504	30 mg bid/20 mg bid	38.1/30.4/19 (16)	21/17.6/4.6(24)	Not assessed
	Palace 2 [105]	484	30 mg bid/20 mg bid	32.1/37.4/18.9 (16)	22.1/18.8/2.7 (16)	Not assessed
	Palace 3 [106]	505	30 mg bid/20 mg bid	41/28/18 (16)	21/20/8 (16)	Not assessed
	Palace 4 [107]	527	30 mg bid/20 mg bid	32.3/29.2/16.9 (16)	-	Not assessed
Secukinumab	Future 1 [110]	606	75 mg[1]/150 mg [1]	50.5/50/17.3 (24)	64.8/61.1/8.3 (24)	wk 24 and wk 52
	Future 2 [111]	397	300 mg[2]/150 mg[2]/75 mg[2]	54/51/29/15 (24)	63/48/ 28 (not sig)/16 (24)	Not assessed
Ustekinumab[3]	PSummit-1 [113,115]	615	90mg/45mg	49.5/42.4/22.8 (24)	62.4/57.2/11 (24)	wk 24 and 2 yrs
	PSummit-2 [114,116]	312	90mg/45mg	43.8/43.7/20.2 (24)	55.6/51.3/5 (24)	wk 24 and 1 yr

[1]placebo or IV loading doses 10 mg/kg at baseline, week 2, and week 4 and then SC every 4 weeks
[2]SC loading doses 300 mg, 150mg, 75 mg, or placebo once a week from baseline to week 4 and then SC every 4 weeks
[3]placebo, 45 mg or 90 mg SC at baseline and 4 weeks and then every 12 weeks
ACR20, American College of Rheumatology 20% improvement criteria; bid, twice a day; IV, intravenous; PASI75, ≥ 75% improvement in Psoriasis Area and Severity Index; SC, subcutaneous; tx, treatment; wk, week; yrs, years

Table 6. Medications in Development for PsA

Drug	Mechanism of Action	Current Phase in Clinical Trials
Ixekizumab	IL-17A inhibitor	SPIRIT-P2 Phase III (NCT02349295)
Abatacept	CTLA4-Ig	phase III (NCT01860976)
Risankizumab	IL-23 inhibitor	phase II (NCT02986373)
Guselkumab	IL-23 inhibitor	phase II (NCT02319759)
Tofacitinib	Oral JAK inhibitor	phase III (NCT01976364)
Tildrakizumab	IL-23 inhibitor	Unknown currently

CTLA4-Ig, cytotoxic T lymphocyte associated antigen-4 immunoglobulin fusion protein