
A short history of biological therapy for psoriatic arthritis

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ABSTRACT

Psoriatic arthritis (PsA) is an inflammatory disease characterised by the clinical domains of arthritis, enthesitis, dactylitis, spondylitis, and psoriasis, often causing significant functional disability, loss of quality of life, and premature mortality. Prior to the introduction of targeted biologic medications, such as TNF inhibitors, the capacity to control disease activity was limited, with only modest effects noted in most patients with traditional oral medications such as methotrexate and sulfasalazine. The introduction of TNF inhibitors substantially changed the outlook of PsA patients, yielding significant response in all relevant clinical domains and demonstrating the capacity to inhibit progressive structural damage of joints. However, not all patients responded to these agents and many patients displayed initial response which waned over time, partly due to immunogenicity (development of antibodies which blocked full therapeutic effect of the biologic protein), or because of poor tolerability and/or adverse events. Thus, it has been important to develop new medicines which target other key cytokines and immunologic pathways, including ustekinumab which inhibits both IL12 and IL23 and thus is felt to work in both the TH1 and TH7 pathways of inflammation, has been approved for the treatment of PsA as well as psoriasis. IL17 inhibitors, including secukinumab and ixekizumab have demonstrated significant effectiveness in psoriasis and PsA; abatacept, which modulates T cell activity via inhibition the second signal of T cell activation is under study. This article provides an historical overview of this revolution; details of specific biological therapies will be provided in adjacent articles in this supplement.

History of biological therapy for psoriatic arthritis

In the 1990s, our deepening understanding of the molecular and cellular pathogenesis of autoimmune inflammatory

diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis, inflammatory bowel disease (IBD), and multiple sclerosis (MS) as well as many others, along with key developments in the capacity to identify and produce protein antibody therapeutics directed at inhibiting specific cytokines and cells, came together to begin the era of “biologic” therapy of autoimmune disease. The first diseases to be targeted were prominent autoimmune diseases in the fields of rheumatology, dermatology, gastroenterology, and neurology, specifically RA, psoriasis, IBD, and MS. Many of the molecular mechanisms driving these diseases have overlapping features and to an extent, development of therapeutics overlapped, in other ways they have diverged, with the finding that drugs that provide efficacy in one disease may not do so in another.

In the field of psoriasis, based on understanding of the key role of T lymphocytes in disease pathogenesis, the first biologic agents to be studied were co-stimulatory blockade agents, agents that inhibit the “second” signal of lymphocyte activation. The initial drugs tested were alefacept and efalizumab. These proved to be modestly efficacious and were approved for the treatment of psoriasis. However, issues such as the potential for reduction of CD4 positive T cells with alefacept, and unexpected episodes of serious infection with efalizumab, leading to its withdrawal, as well as lesser degree of efficacy compared to the next wave of biologics, the TNF inhibitors, led to cessation of use of these agents for psoriasis. Phase 2 studies in PsA showed modest efficacy (1, 2), and thus proof-of-concept for T cell modulation role in PsA, but ultimately approval in PsA was not sought because of poor success in psoriasis.

TNF inhibitors

The introduction of the TNF inhibitors (TNFi), the first biologic agents used

in the treatment of rheumatologic disease, in the late 1990s greatly strengthened the capacity to achieve states of low disease activity or remission for conditions such as RA and the spondyloarthritides, including PsA. In parts of the world where these therapies are affordable, these agents have become the gold standard for management of these diseases. The first proof-of-concept study of TNF inhibition in PsA was with etanercept. In an investigator-initiated study in Seattle, Mease and Goffe explored the efficacy and safety of etanercept in 60 patients with moderate to severe PsA (3).

Given the paucity of previous clinical trials in PsA, there was little in the way of a roadmap for assessing efficacy. The Psoriatic Arthritis Response Criteria (PsARC) had been used in a previous trial of sulfasalazine in PsA (4), otherwise, measures used were derived from RA and psoriasis trials (ACR response criteria, Health Assessment Questionnaire, SF-36, Psoriasis Area and Severity Index (PASI), etc (5). In discussions with the FDA, it was determined that patients already taking methotrexate (MTX) could continue to take this drug, and be stratified to etanercept or placebo.

As it developed, half of the patients in the trial were on background MTX, so the trial naturally yielded 4 similar arms: etanercept *versus* MTX, with or without MTX background. A minimum of 3 tender and swollen joints was allowed, partly in order to understand the response of the oligoarticular form of PsA (many of these design features continue to be used in PsA trials to date). At the 12 week primary endpoint of the study, highly statistically significant improvement was observed in all clinical domains measured in the etanercept arm of the study, and no new safety issues emerged. Presence or absence of background MTX did not influence outcomes.

In parallel, Antoni (Germany) and others were studying infliximab in PsA in a similarly designed trial (6). This too showed significant effect. In addition to arthritis and skin disease, improvement was seen in enthesitis and dactylitis, also key clinical domains in PsA. Sub-

sequent phase 3 trials with these two agents, which included radiographic assessment of joint damage and response to therapy, led to regulatory approval for PsA (7, 8). Soon, other anti-TNFs, including adalimumab, golimumab, and certolizumab pegol were studied, showed similar degrees of effectiveness and safety, and are now approved for PsA (9-11). The science of outcome measurement of PsA has also advanced in parallel, resulting in more refined and reliable assessment (12).

However, even with the success of anti-TNF therapy in general, not all patients achieve or maintain satisfactory states for a variety of reasons. Some patients may have a contraindication to use of TNFi, for example those with multiple sclerosis, and should not have a TNFi initiated. Others may have a "relative" contraindication, such as severe congestive heart failure, lymphoma, or living or working in an area endemic for tuberculosis or invasive fungal infections, in which case the patient or physician may be reluctant to initiate TNFi therapy. A significant number of patients do not respond to TNFi therapy. Depending what one considers a desirable response, in typical clinical trials of TNFi therapy in PsA, at least 40% do not achieve an ACR 20 response, at least 60% do not achieve an ACR 50 response and at least 80% do not achieve an ACR 70 response by 24 weeks of treatment (13). Reasons for primary non-response include true lack of clinical effect, intolerability, serious adverse effects, as well as other issues such as structural damage or the presence of concomitant fibromyalgia which does not respond to immunomodulatory therapy and thus "blunt" assessed therapeutic response.

Sometimes such a "primary" non-responder will have a response when a second TNFi is tried, but registry data suggest that achievement of a good response is not as likely in patients who have demonstrated non-response to trial of a first TNFi. In those who do have a satisfactory response to a first TNFi, we are learning that "survival" on the TNFi, *i.e.* durability of a satisfactory response, can be quite variable, ranging from months to many years. The data for this comes from observations made

in clinical registries, such as the Consortium of Rheumatology Researchers of North America (Corrona) (14), and biologic registries in countries such as Norway (15) and Denmark (16).

It appears that average "survival" of PsA patients on TNFi is in the range of 2-4 years for the first TNFi tried and shorter duration for subsequent TNFi. Reasons for loss of effect of the TNFi appear to be multifactorial. In some, intolerability or serious adverse effects may occur with time, in others, disease activity may change and increase despite the use of the TNFi; and in others, gradual loss of efficacy may occur. Loss of efficacy may be due partly to development of immunogenicity to the therapeutic protein, *i.e.* development of an antibody response which may wholly or partly neutralise treatment effect. This phenomenon has most clearly been documented with chimeric antibody constructs such as infliximab, in which the antibody response may be directed against the murine portion of the molecule (17, 18). Neutralising antibodies appear more likely to occur in monoclonal antibody constructs compared to the soluble receptor construct exemplified by etanercept (17, 18). Concomitant use of methotrexate may inhibit antibody formation against TNFi (17, 18).

Indirect evidence that immunogenicity may shorten duration of TNFi effectiveness is derived from registry studies, in which it has been demonstrated that infliximab survival is shorter in PsA when this agent is used as monotherapy versus used in combination with methotrexate (14, 15). By contrast, this difference has not been noted with etanercept, potentially resulting from less immunogenicity associated with this agent (14). In sum, many PsA patients either do not initially achieve or gradually lose response to TNFi, generating a need for therapies with different mechanisms of action and demonstrated ability to modify disease activity both *de novo* and post TNFi inadequate response. Furthermore, development of therapies with different administration frequency and improved safety profile appeals to patient and physician preference.

A caveat about the above referenced

trials is that there are several disparate ways in which PsA may present clinically. The predominant clinical presentation is polyarticular disease. Some patients may predominantly manifest oligoarticular (<5 involved joints) disease or arthritis mutilans, a rare form in which the distal joints become severely damaged and may dissolve. These subsets have not been adequately assessed in standard clinical trials of PsA. Although subset analysis of trials suggests that these patients also respond to biologic therapy, an in depth study of response has not been conducted.

Axial disease, *e.g.* sacroiliitis, syndesmophyte formation, and facet arthropathy can occur in PsA. Such spondylitis has not been assessed in PsA clinical trials with definitive clinical or imaging metrics due to the variable nature in which spondylitis presents and the amount of effort and resource needed to assess this domain. Thus, our assumptions about treatment of spondylitis in PsA has been derived from outcomes of ankylosing spondylitis trials. There has been very little study of treatment of “early” PsA; most trials have enrolled patients with disease

established for many years. Trials in early patients are now underway.

Targeting the TH17 cell axis in PsA

Studies conducted over the last few years have shown that IL23, IL17, and IL22, key cytokines involved in the pathway of TH17 lymphocyte activation and effector activities (Fig. 1) (19), are richly expressed in psoriatic skin lesions and the blood and synovium of PsA patients. Their roles in pathophysiology include hyperproliferation of keratinocytes, promotion of synovitis, and activation of a variety of effector cells involved in cartilage and bone destruction (20-24). Trials of therapeutic agents which inhibit IL12/23, IL23 and IL17, detailed in other articles in this supplement, demonstrate significant benefit in various clinical domains of psoriasis and PsA (25-27).

Biologic agents approved for RA – are they beneficial for PsA?

Brief descriptions of biologic agents approved for the treatment of RA, that have been tested or are being tested in PsA, which are not detailed in adjacent articles in this supplement are presented below.

Co-stimulatory blockade modulating T lymphocyte function

Abatacept

Abatacept is a co-stimulatory blockade agent which inhibits T cell activation through second signal inhibition. The “first” signal of T cell activation is the interaction between the major histocompatibility complex MHC and the T cell receptor (TCR). A “second” signal is needed for full T cell activation. A number of receptor-ligand pairs act as second signals, including CD80/86 on an antigen presenting cell and CD28 on the T cell surface. The natural inhibitor of this second signal interaction is CTLA4Ig. This molecule is mimicked by abatacept, which by binding to CD80/86, inhibits CD28 binding, thus inhibiting the second signal and reducing T cell activation. Abatacept is approved for the treatment of RA. A phase 2 study of 170 PsA patients, using various doses of the intravenous formulation of abatacept, demonstrated significant improvement of ACR20 response (28). Magnetic resonance imaging (MRI) study of hands or feet at 24 weeks demonstrated improved synovitis, erosion, and osteitis scores. Skin psoriasis responses were modest.

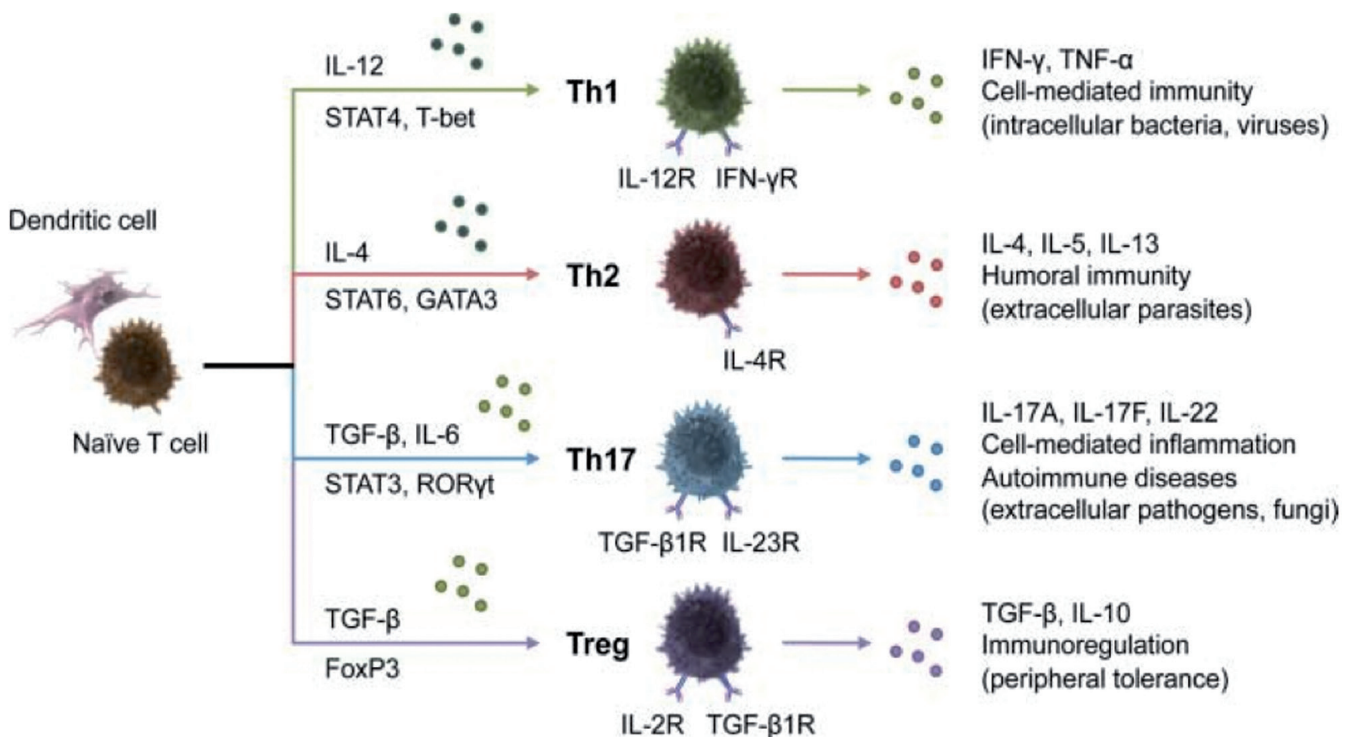


Fig. 1. T Cell differentiation pathways (19).

This medication is now in development in its subcutaneous form for the treatment of PsA.

IL-6 inhibition

Interleukin 6 (IL6) is a pleiotropic pro-inflammatory cytokine which has a significant role in RA pathogenesis and has been demonstrated to be elevated in PsA synovitis and psoriasis skin lesions (29). Tocilizumab, an IL-6 receptor blocker, is approved for RA. Case reports of its use in PsA have shown both positive and negative results (30).

Clazakizumab

Clazakizumab is a direct IL-6 inhibitor that has demonstrated efficacy in RA (31). This agent was studied in a phase 2 trial with 165 PsA patients, 70% of whom were on background MTX (32). ACR20 response was observed in 29/46/52/39% of patients in the placebo/25 mg/100 mg/200 mg monthly groups at the Week 16 primary endpoint, which was statistically significant in the 100 mg group. PASI 75 responses were observed in 12/15/17/5% of placebo/25 mg/100 mg/200 mg groups. Improvements in enthesitis and dactylitis were most noted in the 100 mg group.

The safety profile included issues expected for an IL-6 inhibiting agent, including increased risk for infection and elevation of hepatic transaminases and lipids. Demonstration of apparently greater effect in joints than skin suggests a differential role for IL6 in the pathogenesis of synovitis as compared to psoriasis. A true dose effect was not demonstrated, given the underperformance of the highest dose group, due partly to use of non-responder imputation analysis and a greater number of adverse effects and dropouts in the higher dose group.

B lymphocyte inhibition

Rituximab, which works by ablating B lymphocytes, is approved for the treatment of RA and vasculitis. Although some B cell aggregation has been noted in PsA synovium (33), B lymphocytes are not considered to be as prominent a part of the pathophysiology of PsA as RA. Small cohorts of PsA patients have been treated with rituximab (34,

35) demonstrating modest effect on arthritis; however, virtually no effect on skin psoriasis has been noted.

IL-1 inhibition

Interleukin 1 is a cytokine produced in excessive amounts in inflammatory conditions such as RA and PsA. The biological agent, anakinra, and IL-1 inhibitor, is approved for the treatment of RA, but clinically has proven disappointing and is used primarily for adult onset juvenile arthritis. Anakinra has not been shown to be efficacious in PsA; a placebo-controlled study which included MRI and synovial biopsy assessment did not demonstrate a difference between placebo and anakinra in PsA (36).

Collateral benefits of the development of biologics for the treatment of PsA

Increased interest in PsA globally generated by these treatment advances, as well as funding by government, the pharmaceutical industry, and private donors, has led to an exponential increase of interest in PsA. Increases have been seen in genetic, translational, clinical, outcomes, and treatment research over the last 15 years, as well as educational efforts directed toward clinicians and patients, and interest by regulatory and other governmental bodies. Dafna Gladman has supervised an exemplary PsA clinical registry in Toronto for decades and is now joined by several national clinical registries in countries such as the United States (Corrona), Sweden, Denmark, Norway, United Kingdom, Italy, and numerous other nations and centers. These registries provide important data about the natural history of disease, outcomes, co-morbidities. An international group of investigators from rheumatology and dermatology has come together in an organisation known as GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis). Since its inception in 2003, this group has now grown to over 600 rheumatologists, dermatologists, and other interested stakeholders, including representatives of patient service leagues, to develop and refine a disease core set

and outcome measures in collaboration with the Outcome Measures in Clinical Trials (OMERACT) association, collaborate in translational research, develop evidence-based treatment recommendations, and pursue educational initiatives globally. GRAPPA is a unique example of two different disciplines of medicine, rheumatology and dermatology, working collaboratively in research and education efforts with a disease that crosses over traditional medical discipline boundaries.

Conclusion

Our capacity to achieve therapeutic benefit for the heterogeneous clinical aspects of PsA, including arthritis, enthesitis, dactylitis, spondylitis, and psoriasis has been significantly improved by the introduction of parenteral biologic therapies. The first introduced biologic therapies which inhibit TNF- α have achieved enduring states of low disease activity or remission in many, but not all patients. Furthermore, efficacy may be lost over time due to a number of factors, including issues of tolerability and safety or development of immunogenicity. Thus, it has been important to develop and test biologic agents with a different mechanism of action than TNF inhibition. Agents which have shown effectiveness in psoriasis, as well as PsA thus far tested, and have been approved for use or are in development include those which inhibit IL-12/23 ustekinumab, IL-17 secukinumab, ixekizumab, IL-23 guselkumab, tildrakizumab, BI-655066, co-stimulatory blockade agents – abatacept, as well as other agents with novel mechanisms of action in the therapeutic pipeline. Over time, we have become more sophisticated in our ability to assess disease activity in PsA, which along with our improved understanding of disease pathogenesis and development of drugs targeting key pro-inflammatory pathways, is leading to more rational and targeted treatment and better outcomes for patients with PsA. Research and awareness about PsA has expanded rapidly partly due to the successes achieved by biologic therapy, bringing two disciplines of medicine, rheumatology and dermatology, to work together collaboratively.

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