

# Biologic Therapies for Psoriatic Arthritis

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## Introduction

Psoriatic arthritis (PsA) is a disease with diverse manifestations. Oligoarthritis is a common pattern identified; however, it could take the form of rheumatoid-like disease or inflammatory spondylitis. Distal interphalangeal joint involvement and arthritis mutilans are distinctive features of PsA. Enthesitis and dactylitis should also be aware of. It is important to recognise the different forms of presentation and to realise that therapeutic options are not equally effective across different patterns of PsA.

Moreover, traditional disease modifying anti-rheumatic drugs (DMARDs) have limitations and more effective agents are very much needed. With the advances in the understanding of immunological disturbances in inflammatory arthritis and the success of using anti-TNF in the management of rheumatoid arthritis, investigators have identified biologic agents that have filled at least to some extent the gaps in the treatment of PsA.

Different anti-TNF agents have been reported to be efficacious in treating PsA, which was also supported by systemic reviews and meta-analyses of the data available in the literature<sup>1-4</sup>. Therefore, various anti-TNF agents have been approved in different national regulatory agencies for their indication in PsA. Other non anti-TNF agents have been tested and would be discussed accordingly.

## Anti-TNF in the Management of Psoriatic Arthritis (Table 1)

### Etanercept

A soluble TNF receptor-FC fusion protein, etanercept, was shown to be effective in a relatively small (No. of subject = 60) double blind placebo-controlled study in improving clinical signs (PsARC, ACR20 etc) and inflammatory markers (ESR and CRP)<sup>5</sup>. The efficacy in using 25mg twice weekly etanercept was reconfirmed by a larger scale consisting over 200 patients with PsA<sup>6</sup>. Radiological progression was also shown to be inhibited by the active treatment group in this large scale trial.

### Infliximab

In an open label study of infliximab treatment for PsA, it had significant reduction of inflammation as detected by MRI<sup>7</sup>. This chimeric monoclonal anti-TNF antibody administrated by intravenous infusion was tested in the IMPACT and IMPACT2<sup>8,9</sup>. Signs and symptoms were shown to be significantly improved in the active

treatment group as compared to the placebo. Both the sustainability of its results and the inhibition of radiological progression were further demonstrated in the 2-year extension of IMPACT study<sup>10</sup>.

Table 1.

Agent	Trial	No. Active/control	Duration (weeks)	Outcome	
Etanercept	Mease 2000	30/30	12	PsARC, ACR 20/50	
	Mease 2004	101/104	24	ACR 20, PsARC, HAQ-DI	
Infliximab	Antoni 2005	IMPACT	52/52	16	ACR 20/50/70, PsARC, HAQ-DI
Adalimumab	Antoni 2005	IMPACT 2	100/100	16	ACR 20/50/70, PsARC, HAQ-DI, PASI 50/70/90, SF-36
	Mease 2005	ADEPT	151/162	24	ACR20/50/70, TSS, PsARC, PASI50/70/90, HAQ-DI, SF-36
	Genovese 2007		51/49	24	ACR20/50/70, TSS, PsARC, HAQ-DI, SF-36
Golimumab	Kavanaugh 2009	GO-REVEAL	292/113	24	ACR20/50/70, PASI50/70/90, HAQ-DI, SF-36, NAPS1, MASES

### Adalimumab

Adalimumab is a humanised monoclonal anti-TNF antibody given by subcutaneous injection on every other week. It has been tested in a pivotal trial, ADEPT, which is a 24-week randomised double-blind, parallel group, placebo-controlled trial. It demonstrated significant improvement in joint and skin manifestations<sup>11</sup>. Modified total Sharp score of radiographic structural damage was inhibited at week 24 in the adalimumab arm. Another study conducted in PsA patients who failed DMARDs showed that addition of adalimumab (vs placebo) resulted in improvement in disease control<sup>12</sup>.

### Golimumab

Golimumab is an humanised monoclonal antibody against TNF- $\alpha$ , which is administrated subcutaneously on a monthly basis. Efficacy and safety in using golimumab for the treatment of PsA has been demonstrated in GO-REVEAL, a 24-week randomised placebo controlled trial<sup>13</sup>. Patients with active treatment (golimumab 50mg or 100mg) had significantly higher proportions in achieving ACR20, ACR50 and ACR70. The beneficial effects on skin involvement, nail disease and enthesitis were also documented in this trial.



## Biologic Therapies Other than Anti-TNF

### Alefacept

An approved agent for the treatment of plaque psoriasis, Alefacept, is a fusion protein of the first extracellular domains of human lymphocyte function-associated antigen 3 (LFA-3) and Fc portion of IgG1. Alefacept inhibits T cell activation by blocking co-stimulation CD2-LFA-3. It was tested in a setting of weekly intramuscular injection for 12 weeks in combination of methotrexate<sup>14</sup>. However, statistically significant different improvement was only achieved in ACR 20 but not ACR 50 or ACR 70. An open-label extension was also reported recently<sup>15</sup>. Nevertheless, it has not been accepted as one of the options used in the treatment of PsA.

### Ustekinumab

An inhibitor of interleukin 12/23, ustekinumab binds to the P40 subunit of these two interleukins preventing their binding to the 12R $\beta$ 1 receptor on the surface of T cell, NK cells and antigen presenting cells. It has already been approved for the management of plaque psoriasis. A crossover trial was conducted in 146 PsA subjects, which showed promising results in terms of its efficacy in improving the manifestations of joint inflammation, skin disease, enthesopathy and dactylitis<sup>16</sup>. A larger scale study is needed to confirm its usefulness in the management of PsA.

## Clinical Guidelines and Recommendations

Guidance in using anti-TNF in PsA has been published by professional societies, like the British Society for Rheumatology (BSR)<sup>17</sup>. Patients with pure axial disease are suggested to adopt the guidance similar for patients with ankylosing spondylitis. Patients with peripheral arthritis who continue to have persistent active disease (defined as  $\geq 3$  SJC and  $\geq 3$  TJC on 2 separate occasions 1 month apart) despite an adequate trial of 2 standard DMARDs individually or in combination (sulphasalazine, methotrexate, cyclosporin or leflunomide) should be considered for the use of anti-TNF. Apart from the above key principles, the guidance also provides details on the definition of an adequate trial of DMARDs, exclusion criteria, criteria for withdrawal of therapy and assessment during anti-TNF therapy.

More recently treatment recommendations for PsA have been developed by an international organisation, namely, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)<sup>18</sup>. The recommendations have a comprehensive coverage of clinical manifestations of PsA including peripheral arthritis, skin and nail diseases, axial disease, dactylitis and enthesitis. It is apparent that the use of biologics in particularly anti-TNF is recommended in patients with moderate to severe degree of all these manifestations (Table 2).

Despite of all these enthusiasms, one should remember the potential adverse effects that may happen with the use of anti-TNF. Infections, in particularly tuberculosis (TB), are known complications. Proper TB screening has been proved to significantly lower the risk of developing TB during the course of anti-TNF therapies. Clinical assessment of cardiac function and the possibility of having an underlying malignancy or an autoimmune disorder such as lupus should all be carried out. Pre-treatment serologic testing for hepatitis B and C status are also required.

## Conclusion

The treatment of PsA has significantly changed by the development of biologic therapies. Clinicians should all be aware of the erosive and progressive nature of PsA. All patients with moderate to severe disease should not be denied of the chance for a better control of their disease by using biologic therapies if clinically appropriate. Therefore, early detection, early treatment and timely referral to specialists could not be over-emphasised.

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Table 2

Systemic Rx	Peripheral arthritis	Skin and nail disease	Axial disease	Dactylitis	Enthesitis
NSAID	✓	x	✓	✓	✓
DMARDs	SSZ, MTX, CycA, LEF	MTX, CycA	x	?	?
Biologics	Anti-TNF	Anti-TNF, Alefacept	Anti-TNF	Anti-TNF	Anti-TNF