P&T Committee Brief

Targeted Immune Modulators: *Comparative Drug Class Review*

Alison Little, MD
Center for Evidence-based Policy
Oregon Health & Science University
3455 SW US Veterans Hospital Road, SN-4N
Portland, OR 97239

Tel: 503.494.2182
Fax: 503.494.3807
www.ohsu.edu/policycenter

This brief was written by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). It is a summary of certain material matters contained in the Drug Effectiveness Review Project (DERP) report "Drug Class Review on Targeted Immune Modulators" dated March 2012, which is a product of the UNC-RTI Evidence-based Practice Center at the University of North Carolina at Chapel Hill. You can find the original report online at the following web address: http://derp.ohsu.edu/about/final-document-display.cfm. Although at least one of the authors of this report reviewed and commented on the brief, its contents and conclusions are those of the Center and not those of the authors or reviewers of the DERP report. The Center is a policy resource and is not providing any legal or business advice. This Brief is subject to the information and conclusions contained in the DERP report, and readers of this Brief are advised to review the DERP report. This Brief is intended for the benefit of the participant organizations and their constituent decision-making bodies.

Targeted Immune Modulators

Targeted immune modulators (TIMs), commonly referred to as biological response modifiers, or simply *biologics*, are a relatively new category of medication used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Chrohn's disease (CD), ulcerative colitis (UC), and plaque psoriasis (PP). The US Food and Drug Administration (FDA) approved the first of the biologics (infliximab) in 1998. Since then, the FDA has approved 12 additional agents for treating various rheumatic conditions, inflammatory bowel disease (IBD), and psoriasis. TIMs work by selectively blocking a variety of different mechanisms involved in the inflammatory and immune response. Biologics available in the US and Canada, and their indications, route, and frequency of administration are listed in Table 2.

Purpose

The purpose of this review is to compare the efficacy, effectiveness, safety, and tolerability of the included drugs in patients with RA, JRA, AS, PsA, CD, UC, and PP.

Methodology

The Drug Effectiveness Review Project (DERP) reviews all pertinent studies, solicits and accepts public input, and updates reviews frequently. The original TIMs review was completed in 2005 and has been updated twice previously. Literature searches for this update identified 1,589 additional citations, and five dossiers were received from manufacturers. Study eligibility is determined by pre-set criteria, and studies which did not meet these criteria with respect to study design or duration, patient population, interventions, outcomes, language of publication, or appraised quality were excluded. Included health outcomes are listed in Table 1.

Table 1. *Included Health Outcomes*

Health Outcomes	▪ Quality of life (QOL) ▪ Functional capacity ▪ Pain ▪ Reduction in # of swollen or tender joints ▪ Response ▪ Remission ▪ Reduction of affected body surface area (Psoriasis Area & Severity Index) ▪ American College of Rheumatology scales (ACR 20/50/70) ▪ Hospitalizations ▪ Mortality ▪ Steroid withdrawal
Radiological Outcomes	Considered only if no studies of other health outcomes were found
Safety Outcomes	▪ Overall serious and specific adverse events (AEs) ▪ Withdrawals due to AEs

Evidence Available

Relevant information for this topic consists of 163 unique studies, 68 of them new in this update: 70 randomized controlled trials (RCTs), 51 observational studies, 31 systematic reviews, and 11 trials of other design.

Table 2. *Biologics Available in US & Canada*

Generic Name	Trade Name	Indication	Route & Frequency of Administration
abatacept[1]	Orencia®	RA JIA	IV infusion Q 2-4 weeks, *or* SQ injection Q week
adalimumab[2,3]	Humira®	RA PsA AS JIA CD PP	SQ injection Q 1-2 weeks
alefacept	Amevive®	PP	IM injection Q week
anakinra	Kineret®	PP	SQ injection Q week
certolizumab pegol[3]	Cimzia®	RA CD[4]	SQ injection Q 2-4 weeks
etanercept[1,3]	Enbrel®	RA PsA AS JRA PP	SQ injection 1-2X/week
golimumab[3]	Simponi®	RA PsA AS	SQ injection Q month
infliximab[1,3]	Remicade®	RA CD PsA AS active UC PP	IV infusion Q 4-8 weeks
natalizumab	Tysabri®	CD[4]	IV infusion Q 4 weeks
rituximab	Rituxan®	RA	IV infusion at 0 and 15 days, then Q 16-24 weeks
tocilizumab[1]	Actemra®	RA JIA[5]	IV infusion Q 2-4 weeks
ustekinumab	Stelara®	PP	SQ injection at 0 and 4 weeks, then Q 12 weeks

[1] *approved for use in children in the US & Canada*
[2] *approved for use in children in the US only*
[3] *TNF inhibitor*
[4] *not approved for CD in Canada*
[5] *not aoproved for JIA in Canada*

Key Questions & Findings

Question 1 *How do the included drugs compare in their effectiveness for alleviating symptoms and stabilizing the disease in patients with RA, JRA, AS, PsA, Crohn's disease, UC, and plaque psoriasis?*

Rheumatoid Arthritis

Currently, the following drugs are approved by the FDA and Health Canada (HC) for the treatment of RA: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab. The only double blind head-to-head study found compared abatacept to infliximab in patients with inadequate response to methotrexate. At six months no differences in efficacy were apparent, but after one year abatacept was significantly more efficacious on most outcome measures than infliximab. ***Of note: infliximab was administered at a fixed dose throughout the entire study, even though infliximab efficacy trials have shown that up to 30% of patients require dose increases.***

Other direct comparisons of targeted immune modulators for the treatment of rheumatoid arthritis were limited to one small RCT and multiple non-randomized or observational studies rendering evidence of low strength. These studies indicated no differences in efficacy between adalimumab (two observational studies) and etanercept (five observational studies, one RCT, and one non-randomized trial) compared with infliximab.

Table 3. *Comparative Efficacy for RA*

Based on Direct Evidence
abatacept > infliximab
adalimumab ~ etanercept
adalimumab > infliximab
etanercept > infliximab
Based on Indirect Evidence
etanercept > abatacept/anakinra/infliximab/tocilizumab
adalimumab ~ anakinra/infliximab/tocilizumab

> = more efficacious than
~ = has similar efficaciousness to
< = less efficacious than

Indirect comparisons of randomized placebo-controlled trials suggest that etanercept is statistically more efficacious than abatacept, anakinra, infliximab, and tocilizumab (range of relative risks from 2.31 to 3.30). No statistically significant differences in efficacy could be detected among adalimumab, anakinra, infliximab, and tocilizumab. Data were too heterogeneous to conduct indirect comparisons of certolizumab pegol, golimumab, and rituximab with other TIMs. Good to fair evidence exists from meta-analyses and large RCTs that abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab are statistically significantly more efficacious than placebo for the treatment of RA. Treatment effects are large and consistent across studies.

Juvenile Idiopathic Arthritis

Currently, abatacept, adalimumab, etanercept, and tocilizumab are approved by the FDA and HC for the treatment of JIA. No evidence on the comparative effectiveness of any TIM for the treatment of JIA exists. Five RCTs provide fair evidence that abatacept, adalimumab, etanercept, infliximab, and tocilizumab are more efficacious than placebo for the treatment of JIA.

Ankylosing Spondylitis

Adalimumab, etanercept, golimumab, and infliximab are currently approved by the FDA for the treatment of AS (only etanercept and infliximab are approved for the treatment of AS in Canada). No direct evidence on the comparative effectiveness of TIMs for the treatment of AS exists. The strength of the evidence is insufficient. Good to fair evidence exists for the general efficacy of adalimumab, etanercept, golimumab, and infliximab compared with placebo for the treatment of AS, based on one systematic review of nine RCTs (adalimumab, etanercept, and infliximab), and four other RCTs (etanercept, golimumab, and infliximab). No studies on abatacept, alefacept, anakinra, certolizumab pegol, natalizumab, rituximab, tocilizumab, or ustekinumab for the treatment of AS were found.

Psoriatic Arthritis

The following drugs are currently approved by the FDA and HC for the treatment of PsA: adalimumab, etanercept, golimumab, and infliximab. No head-to-head trials comparing one TIM to another were found, nor were any studies on anakinra, certolizumab pegol, natalizumab, rituximab, tocilizumab, or ustekinumab. Two systematic reviews conducted indirect comparisons of adalimumab, etanercept, and infliximab for the treatment of PsA in adults. Both analyses suggested that the three treatments are more efficacious than placebo, but no statistically significant differences among them could be detected. One prospective observational registry study of 595 patients with PsA showed that adalimumab, etanercept, and infliximab have similar positive effects on QOL. The strength of evidence for this comparison is considered low. In addition, evidence from one phase II study indicated that alefacept combined with methotrexate is more efficacious than methotrexate alone and that abatacept, golimumab, and ustekinumab are more efficacious than placebo. No studies that evaluate the use of TIMs in children with PsA were found.

Ulcerative Colitis

Only infliximab is currently approved by the FDA and HC for the treatment of UC. No comparative evidence was found for TIMs in the treatment of UC, and the evidence is considered insufficient. One systematic review (five RCTs) found that infliximab is significantly more efficacious than placebo for the treatment of UC. No trials in children were found.

Plaque Psoriasis

Adalimumab, alefacept, etanercept, infliximab, and ustekinumab are currently approved by the FDA and HC for the treatment of plaque psoriasis. One head-to-head RCT comparing etanercept to ustekinumab found that significantly more patients in the ustekinumab group achieved the primary outcome of a PASI 75 response compared to etanercept. The strength of the evidence for this comparison is low. Multiple placebo controlled trials (17) provide good to fair evidence of the general efficacy of adalimumab, alefacept, etanercept, infliximab, and ustekinumab for the treatment of plaque psoriasis. No studies on the other TIMs were found. One study of etanercept in children found a greater response compared to placebo.

Question 2 *What are the comparative incidence and severity of complications associated with the use of these drugs?*

Eighteen head-to-head studies provided direct evidence on the harms associated with TIMs, which was supplemented by indirect comparisons of over 200 RCTs (placebo or active control). Evidence on the comparative risks of serious infection with TIMs was low strength. Evidence from short-term trials (median six months duration) using indirect comparison meta-analyses indicated serious infections are less common with abatacept than with certolizumab pegol, infliximab, and tocilizumab, while certolizumab pegol appeared to have a higher risk than adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, or placebo. Analyses of only the antitumor necrosis factor (anti-TNF) drugs (adalimumab, certolizumab pegol, golimumab, and infliximab) indicated as a group they have an increased risk compared to control groups, while the other TIMs, including etanercept (which works via a different mechanism to antagonize anti-TNF than the previous group) did not. Limited observational evidence indicates an increased risk of serious infection with anti-TNF drugs etanercept, infliximab, and adalimumab, and that the risk was highest in the first six months of treatment. The risk of tuberculosis appeared to be elevated with the use of TIMs as a group based on trial data. Comparisons between the drugs are more limited, with the best evidence indicating increased risk of tuberculosis with adalimumab compared with etanercept, and a nearly statistically significant increased risk with infliximab compared with etanercept.

On the whole, a broad range of evidence did not indicate a clear increase in risk of malignancy in general with the use of TIMs. There was evidence suggesting that the risk of nonmelanoma skin cancer is increased with the use of the anti-TNF drugs adalimumab, infliximab, and etanercept. Observational evidence supported these findings, although the risk estimates are somewhat lower magnitude. The strength of evidence comparing the risk of malignancy with TIMs is low. Although the FDA has issued a warning about the potential increased risk of malignancy in children, evidnce in children is insufficient for making conclusions. While case reports have indicated potential risk of various other

serious adverse events, strength of evidence on the comparative risk of heart failure, autoimmunity, demyelination, and serious hepatic events with TIMs is insufficient at this time.

Table 4. *Comparative Harms*

Infections
abatacept > certolizumab pegol/infliximab/tocilizumabnfliximab (serious infection)
certolizumab > adalimumab/anakinra/etanercept/golimumab/infliximab/rituximab (serious infection)
TIMs [in general] > control groups (TB)
adalimumab > etanercept (TB)
infliximab > etanercept (TB)
Malignancy
adalimumab/infliximab/etanercept > control groups (nonmelanoma skin cancer)
Overall AE/Discontinuation Due to AE
abatacept/anakinra < other TIMs (serious AE)
infliximab > abatacept/adalimumab/etanercept/golimumab (discontinuation due to AE)

> = higher risk than
< = lower risk than

Comparative evidence on overall AEs, discontinuation of drug due to AEs, and other measures of short-term tolerability was low to moderate strength, depending on the specific outcome. The rates of overall AEs occurring with TIMs did not differ statistically significantly between the drugs. In short-term trials abatacept and anakinra had lower risk of a serious AE compared to other TIMs. Infliximab had a higher risk of patients discontinuing treatment due to AEs compared with abatacept, adalimumab, etanercept, and golimumab at least partially due to the increased risk of infusion or allergic reactions. Evidence on the comparative risk of AEs associated with TIMs in children is very limited and was of insufficient strength to make conclusions. The AE profiles appeared similar to those seen in adults.

Question 3 *Do the included drugs differ in effectiveness or AEs in the following subgroups: racial groups, genders, age groups; or in patients taking other commonly prescribed drugs?*

Overall, the strength of evidence to determine differences between TIMs in effectiveness or AEs among subgroups was insufficient. The majority of the studies were not specifically designed to compare the effectiveness and safety of TIMs in one subgroup of patients compared to another. However, subgroup analyses and indirect evidence provided evidence for some TIMs in certain subpopulations. Evidence on the effect of age was mixed. Indirect evidence from three studies indicated that age is not associated with greater or less clinical response rates or AEs in AS, RA, PsA, or PP. However, three other studies found differences; in one case, response to treatment of RA with etanercept and infliximab was better in those over less than 65 years, in two others there was a higher risk of AEs in older patients.

Regarding race, indirect evidence showed that adalimumab and ustekinumab had better response rates compared with placebo in Asian patients with PP, while patients of non-white ethnicity had a six-fold increased risk of tuberculosis compared with white patients treated with anti-TNF drugs for RA. The evidence on gender differences is limited to two studies, one reporting on efficacy and the other on AEs. A pooled analysis of nine efficacy studies of alefacept did not detect any differences in efficacy and safety for obese or diabetic patients with PP. Two studies reported no differences in AEs in patients with comorbidities while three studies reported an increased risk of the occurrence of AEs.

Conclusion

In summary, insufficient evidence exists for the comparative effectiveness of TIMs for the treatment of JIA, AS, CD, and UC. For RA there is a moderate strength of evidence that there is no difference in efficacy between abatacept and infliximab, but that etanercept is more effective than infliximab. In addition, there is low strength of evidence that etanercept is more efficacious than abatacept, anakinra, and tocilizumab, and that the following comparisons have similar efficacy:

- Abatacept is similar to adalimumab, anakinra & tocilizumab
- Adalimumab is similar to anakinra & tocilizumab
- Anakinra is similar to infliximab & tocilizumab
- Infliximab is similar to tocilizumab

For the treatment of PsA there is low strength of evidence that there is no difference in effectiveness between adalimumab, etanercept, and infliximab; and for the treatment of PP there is also low strength of evidence that ustekinumab is more efficacious than etanercept.

For harms there is low strength of evidence that serious infections are less common with abatacept than with the other drugs, and that certolizumab pegol has greater odds of serious infection than adalimumab, anakinra, etanercept, golimumab, infliximab, and rituximab. In addition, adalimumab, etanercept, and infliximab have a higher risk of serious infection than non-TIM therapies, and the risk of tuberculosis is higher with adalimumab than etanercept. There is also low strength of evidence that the risk of non-melanoma skin cancer is greater with adalimumab, etanercept, and infliximab compared to non-TIM therapies, but no differences between TIM drugs was found. For other AEs the following comparisons had a low strength of evidence:

- Adalimumab has a lower rate compared to infliximab & etanercept for overall AEs
- Infiximab has a higher rate compared to adalimumab & etanercept for overall AEs
- Etanercept has similar rates of overall AEs to ustekinumab, although injection site reactions are higher for etanercept
- Abatacept and anakinra have lower risk of serious AEs than other TIMs in the short-term
- Discontinuations due to AEs are higher with infliximab compared to abatacept, anakinra, etanercept & golimumab, due in part to a higher rate of infusion reactions

There was insufficient evidence for all other comparisons, including efficacy and harms in children and subpopulations.