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Class Update: Biologicals for RA, Psoriasis and Crohn’s Disease

Month/Year of Review: September 2014

End date of literature search: August 2013

New drug(s): apremilast (Otezla®)
Vedolizumab (Entyvio®)

Manufacturer: Celgene
Takeda Pharmaceuticals

Current Status of PDL Class:

Generic Name	Trade Name	PDL Status	Indication
Abatacept	Orencia®	Non-preferred	RA, Juvenile RA, Juvenile idiopathic arthritis
Adalimumab	Humira®	Preferred	RA, Psoriatic arthritis, ankylosing spondylitis, Juvenile idiopathic arthritis, Crohn’s disease, Plaque psoriasis, ulcerative colitis
Anakinra	Kineret®	Non-preferred	RA, Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
Certolizumab	Cimzia®	Non-preferred	RA, Crohn’s disease, psoriatic arthritis, ankylosing spondylitis
Etanercept	Enbrel®	Preferred	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis
Golimumab	Simponi®	Preferred	RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Infliximab*	Remicade®	Non-preferred	RA, Crohn’s disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis
Natalizumab*	Tysabri®	Non-preferred	Crohn’s disease
Rituximab*	Rituxan®	Non-preferred	RA
Tocilizumab*	Actemra®	Non-preferred	RA, juvenile idiopathic arthritis
Tofacitinib	Xeljanz®	Non-preferred	RA
Ustekinumab	Stelara®	Non-preferred	Plaque psoriasis, Psoriatic arthritis
Vedolizumab	Entyvio	Non-preferred	Ulcerative colitis, Crohn’s disease

Abbreviations: RA, rheumatoid arthritis

* Must be billed via J-code and payment requires trial of preferred self-administered drug first.

Research Questions:

- Is there new comparative evidence that Targeted Immune Modulators (TIMs) differ in effectiveness for patients with Rheumatoid Arthritis (RA), Psoriatic arthritis (PsA), Crohn’s disease, plaque psoriasis, ulcerative colitis (UC), ankylosing spondylitis, or Juvenile idiopathic arthritis?
- Is there any new evidence that TIMs differ in harms?
- Is apremilast more effective or safer than currently available agents for the treatment of plaque psoriasis?

Conclusions:

- There remains low to insufficient evidence of any difference in efficacy between TIMs in the treatment of RA. The most obvious differences that might be clinically relevant involve dosage and administration (oral, intravenous, subcutaneous).¹
- There is insufficient comparative evidence for the efficacy of TIMs in the treatment of juvenile idiopathic arthritis, ankylosing spondylitis, UC, and Crohn's disease.¹
- There is insufficient evidence based on 1 randomized controlled trial of no difference in efficacy between adalimumab, etanercept and infliximab for the treatment of PsA.¹
- There is insufficient evidence based on indirect comparisons of no difference between etanercept, adalimumab and abatacept in preventing disease flares for the treatment of juvenile idiopathic arthritis.
- For the treatment of Crohn's disease, TNF inhibitors (infliximab, adalimumab and certolizumab) were more effective than placebo in inducing remission (RR 1.8; 95% CI 1.4 to 2.4; moderate SOE). However, infliximab is the only biological consistently favored over placebo for multiple outcomes and at multiple time points for both induction and maintenance of remission.²
- There is moderate quality evidence that apremilast 20mg twice daily and apremilast 30 mg twice daily improves signs and symptoms of PsA, as measured by the ACR20 response, compared to placebo (32%, 37%, and 19%, respectively). There appears to be a small advantage of apremilast 30mg twice daily dose; however it has not been proven to be statistically superior to 20mg twice daily.
- There is moderate to high quality evidence that vedolizumab is significantly superior to placebo for induction of clinical remission, clinical improvement and prevention of clinical relapse in patients with moderate to severe UC with similar risk of adverse events.³
- There is moderate quality evidence of a significantly superior effect of vedolizumab on clinical remission compared to placebo, although the improvement was modest at best. In patients with failure of previous TNF inhibitor, there is low quality evidence of no difference in clinical remission at week 6 between vedolizumab and placebo.
- There is low quality evidence that vedolizumab is significantly superior to placebo for maintenance of clinical remission at week 52 compared to placebo.

Recommendations:

- Modify prior authorization criteria to include new FDA approved indications and new medications.
- Evaluate comparative costs of newly approved agents in executive session; Make golimumab non-preferred.

Reason for Review:

A new Drug Effectiveness Review Project (DERP) report was published, two new drugs were approved, and new FDA approved indications were granted for multiple TIMS. This update will evaluate and summarize this new evidence.

Previous P&T Conclusions (November 2011^{2,3}):

- There is low quality evidence of no conclusive differences in disease activity (ACR 50) between TIMs for the treatment of RA.
- There is moderate quality evidence of improvements in disease activity from combination therapy of a TIM plus methotrexate compared to monotherapy in the treatment of RA.
- There is insufficient evidence comparing individual TIMs to make conclusions for the treatment of chronic plaque psoriasis.
- There is low strength evidence favoring individual TIMs versus non-biologic agents (methotrexate) in the treatment of plaque psoriasis.
- There is insufficient direct evidence comparing tofacitinib to other proven agents for the treatment of RA.
- There is moderate quality evidence that tofacitinib decreases symptoms compared to placebo, as measured by the ACR20 response and increases physical functioning at 3 months in patients with active RA who had prior inadequate response or intolerance to non-biologic or biologic DMARDs.

Background:

Targeted immune modulators (TIMs) are used in the treatment of immunologic and inflammatory diseases, including rheumatoid arthritis (RA), juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis (PsA), plaque psoriasis, Crohn's disease, and ulcerative colitis (UC).¹ They work by selectively blocking mechanisms involved in the inflammatory and immune response and include: Tumor necrosis factor (TNF) inhibitors (adalimumab, certolizumab, golimumab, etanercept and infliximab), interleukin-1 blockers (anakinra), and other monoclonal antibodies (abatacept, alefacept, natalizumab, rituximab, ustekinumab and tocilizumab). Tofacitinib was the first oral Janus kinase (JAK) inhibitor approved.

Apremilast is an oral type 4 phosphodiesterase (PDE4) inhibitor indicated for the treatment of psoriatic arthritis. PDE 4 is a key enzyme in the degradation of cyclic adenosine monophosphate (cAMP), an intracellular second messenger that plays an important role in controlling a network of pro-inflammatory and anti-inflammatory mediators.¹ By inhibiting PDE4, the production of TNF-alpha is reduced.

RA is an autoimmune disease that involves inflammation of the synovium with progressive erosion to bone leading in most cases to misalignment of the joint, loss of function, and disability. Treatment goals are to control pain and inflammation, and ultimately, remission or at least low disease activity.¹ Therapies for RA include corticosteroids, oral disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. Methotrexate is the most commonly used DMARD because of its proven efficacy and well understood long-term effects. In patients with persistent disease despite aggressive management with oral agents, biologic agents, often in combination with methotrexate are considered the standard of care. Juvenile idiopathic arthritis occurs in children under the age of 16. NSAIDs are first line therapy, followed by oral DMARDs, and biologic agents. Abatacept, adalimumab etanercept, and tocilizumab are approved for the treatment of juvenile idiopathic arthritis.

Primary endpoints used in the clinical trials are the American College of Rheumatology (ACR) response, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Disease Activity Score 28 (DAS-28). The ACR response is a composite endpoint with seven components used to calculate the proportion of patients achieving a target percentage of improvement from baseline and is considered a measure of efficacy and overall disease activity. Patients are said to

meet ACR 20 criteria when they have at least 20% reductions in tender and swollen joint counts and in at least 3 of the domains. ACR 50 and ACR 70 criteria are similar, but with improvement of at least 50% and 70% in individual measures.⁴ The FDA accepts ACR 20 response as an acceptable demonstration of efficacy supporting a clinical response claim, and ACR 70 response lasting for 6 months as supportive of a claim of a major clinical response.³ ACR 50 and ACR 70 are considered more clinically significant than ACR 20. The HAQ-DI is a widely used self-report measure of functional capacity. Scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.⁴ According to the FDA, the minimal clinically important difference is 0.25 units for a given patient or 0.22 units based on group means. The DAS is another index of disease activity (similar to the ACR response). A DAS-28 score >5.1 corresponds to high disease activity and <3.2 of low disease activity. A score of 2.6 is considered to correspond to remission. The van der Heijde modified Total Sharp Score (mTSS) is a radiographic scoring system for RA joint damage and a change in joint damage of 5.0 is considered minimally clinically important.^{4,5}

Ankylosing spondylitis is a chronic inflammatory arthritis with primary involvement of the axial skeleton and prominent involvement of the spine and sacroiliac joints. Biologic agents targeted TNF are recommended as standard treatment along with DMARDs.

Plaque psoriasis is a chronic autoimmune skin disease which utilizes TIMs for the management of disease. Localized disease may be managed with topical agents, while patients with more widespread disease often require systemic treatment. The American Academy of Dermatology guidelines recommends the use of either biologic or nonbiologic systemic agents or phototherapy in patients with widespread disease, with no clear guidelines for selecting first-line therapy.⁶ Methotrexate is the most commonly prescribed nonbiologic systemic treatment for psoriasis worldwide.

Psoriatic arthritis is an inflammatory arthritis closely associated with psoriasis. The goal of treatment is to suppress joint, tendon and enthesal inflammation, and to manage the skin manifestations. Current treatment involves early use of DMARDs and TNF inhibitors in active and progressive disease. These agents are recommended when the person has peripheral arthritis with 3 or more tender joints and 3 or more swollen joints, and the PsA has not responded to adequate trials of at least 2 standard DMARDs, given on their own or together.⁷

Crohn's disease is a type of inflammatory bowel disease. Biologic agents approved for treatment include infliximab, natalizumab, adalimumab, certolizumab, and most recently vedolizumab. Goal of treatment is to induce and then maintain remission. Controversies in the treatment exist and it is unclear if it is better to take immunomodulators and biologics early (top-down therapy) as opposed to taking them after prolonged steroid use (step-up therapy).

UC is a chronic disease with mucosal inflammation within the colon, historically treated with 5-aminosalicylic acid, corticosteroids and oral immunosuppressants with goals of achieving clinical or mucosal remission. When these are ineffective, TNF inhibitors are another option. Infliximab and adalimumab are most commonly used for UC. Recently the U.S. Food and Drug Administration (FDA) expanded the approved use of adalimumab and golimumab to include treatment of moderate-to-severe ulcerative colitis (UC) in adults, and approved the new agent vedolizumab. Previously, infliximab was the only TIM approved for this indication. The treatment goals in UC are to reduce and maintain remission of symptoms and inflammation and prevent complications.¹ Distal disease may be treated with topical agents and mild disease can be controlled with oral and/or topical 5-aminosalicylate drugs. The American College of Gastroenterologists recommends treatment with infliximab for moderate to severe UC for patients who are steroid refractory or steroid dependent. The Mayo Score is a disease activity index that includes endoscopy and one of the most widely used of the indices in clinical trials.⁸ It takes into account sum of stool frequency, rectal bleeding, mucosal appearance, and physician's global assessment. The FDA has recognized a definition of remission as a Mayo Clinic Score ≤ 2.7 . This definition is

considered less stringent than other endpoints used in clinical trials.⁹ Vedolizumab is a new monoclonal antibody FDA approved for the treatment of UC and Crohn's disease. It affects $\alpha4\beta7$ integrin and inhibits leukocyte adhesion to its counter receptors.

Methods:

The DERP report searched Ovid MEDLINE through November 2013 for head to head evidence, including randomized controlled trials (RCTs) comparing any of the TIMs. An additional search through August 2014 was done. Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

1. The DERP drug class review systematically compared the efficacy, effectiveness, and harms of the TIMS through a literature search through November 2013.¹ Only data from head-to-head trials and systematic reviews with direct comparisons were included in the analysis, which included 15 head-to-head RCTs and 22 head-to-head observational studies. Overall, the authors found low or insufficient evidence for most comparisons about the efficacy, effectiveness, and harms of TIMs. The most obvious differences that might be clinically relevant involve dosage and administration (oral, IV, or SubQ). Results were divided by disease state.

Rheumatoid Arthritis:

- Single head to head trial evidence shows that efficacy outcomes are similar between abatacept and adalimumab, adalimumab and etanercept, adalimumab and tofacitinib, and etanercept and tocilizumab (low to insufficient strength of evidence [SOE]). The evidence is mixed regarding differences in efficacy between adalimumab and tofacitinib.
- There was one double-blind, head to head trial demonstrating no differences in efficacy between patients treated with abatacept or infliximab after 6 months (low SOE).
- Low SOE, based on 1 open-label RCT, of no difference in efficacy between abatacept and adalimumab.
- Low SOE, based on 1 RCT, of similar efficacy between adalimumab and tofacitinib.
- The majority of trials enrolled patients who had failed at least 1 DMARD and some enrolled those who had also failed an TNF inhibitor.

Juvenile Idiopathic Arthritis:

- Insufficient comparative evidence.

Ankylosing Spondylitis

- Insufficient comparative evidence.

Psoriatic Arthritis

- Insufficient evidence based on 1 RCT of no difference in efficacy between adalimumab, etanercept and infliximab.

Crohn's disease

- Insufficient evidence, based on 1 RCT, that switching from infliximab to adalimumab had higher treatment discontinuation and termination rates compared with maintaining infliximab.
- Insufficient comparative evidence for other medications.

Ulcerative Colitis

- Insufficient comparative evidence.

Plaque Psoriasis

- Low SOE, based on 1 head to head RCT, that ustekinumab is more efficacious than etanercept.

The most comparative evidence on harms was available for the tumor necrosis factor inhibitors adalimumab, etanercept, and infliximab. Infliximab had a higher risk of patients discontinuing treatment due to adverse events compared with adalimumab and etanercept (moderate strength of evidence) and more serious adverse events than abatacept (low strength of evidence). Injection site reactions were less frequent for patients receiving abatacept compared with adalimumab and infliximab (low strength of evidence). There was moderate SOE that infliximab has a higher risk of serious infections compared with abatacept, adalimumab and etanercept.

2. A systematic review and network meta-analysis of TNF-alpha inhibitors, including adalimumab, etanercept, golimumab and infliximab, for the management of active PsA was published in 2014.¹⁰ The quality of the including RCTs were assessed according to the NICE guidelines. Twelve RCTs met inclusion criteria and were included in the systematic review, but only 7 were homogenous enough to be included in a meta-analysis. The fixed-effect meta-analysis demonstrated all 4 agents to be significantly better than placebo in response measured by the Psoriatic Arthritis Response Criteria (PsARC). Etanercept and infliximab were significantly more effective than placebo in improving change in Health Assessment Questionnaire (HAQ), while golimumab was not significantly better than placebo. Golimumab was also not significantly better than placebo in improving HAQ scores in patients who had achieved a PsARC response (WMD -0.06; 95% CI -0.18 to 0.06). An incremental analysis based on clinical efficacy and cost-effectiveness was also done. Based on this, golimumab was dominated by etanercept, as etanercept costs less and is more effective; adalimumab was dominated by etanercept; and etanercept was found to be cost-effective intervention. Infliximab was not cost-effective compared with etanercept.
3. A high-quality systematic review using indirect comparisons evaluated the efficacy of biological agents in juvenile idiopathic arthritis.¹¹ All RCTs with biological agents were included, irrespective of trial design. Overall, 11 different trials were included in the analysis. Indirect comparisons found no significant difference between etanercept and adalimumab in disease flare (RR 0.92; 95% CI 0.39 to 2.18). In addition, indirect comparisons found no significant difference between anakinra, tocilizumab and canakinumab in achievement of a ACR30 response. There were no trials that directly compared biological agents to each other.
4. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review for pharmacologic therapies for the management of Crohn's Disease.² Overall, there were a number of medications that were proven to be effective in inducing and maintaining remission in Crohn's disease,

but no single medication or class of medications was proven to be the most effective. TNF inhibitors (infliximab, adalimumab and certolizumab) were more effective than placebo in inducing remission (RR 1.8; 95% CI 1.4 to 2.4; moderate SOE). Infliximab was found to have the greatest consistency on disease activity compared to placebo and had high SOE for fistula healing. There was also low SOE that the combination of infliximab and methotrexate was favored over infliximab alone for disease activity. Infliximab also had the most evidence for maintenance of remission and adalimumab was also favored over placebo. There was low to insufficient evidence for all safety-related outcomes. Older patients and non-whites were underrepresented in clinical trials and outcomes were limited to scales not used in clinical practice. There was insufficient evidence to compare step-up versus top-down treatment and to evaluate treatment in newly diagnosed patient.

5. A systematic review of the effectiveness of newer biological therapy (vedolizumab, abatacept, visilizumab, golimumab) for active moderate to severe UC. Was published in January 2014.¹² Eight RCTs met inclusion criteria; all with moderate methodological quality. Two studies showed improved clinical response in the induction phase for vedolizumab compared to placebo (RR 1.82; 95% CI 1.43 to 2.31), as well as improved clinical remission (RR 2.66; 95% CI 1.63 to 4.34). Two studies also demonstrated superior clinical response with golimumab compared with placebo in the induction phase (RR 1.69; 95% CI 1.41 to 2.03), but not a statistically significant improvement in clinical remission compared to placebo (RR 1.95; 95% CI 0.81 to 4.68). Abatacept appeared to be less effective than placebo in the induction phase.
6. A high quality meta-analysis evaluating TNF inhibitors as treatment for UC intolerant or refractory to conventional medical therapy was published in January 2014.¹³ A literature search through July 2013 identified RCTs comparing TNF inhibitors with placebo or other intervention. The primary outcome was clinical remission. Eight trials were included in the meta-analysis; all evaluating adalimumab and/or infliximab to placebo, corticosteroids, or cyclosporine. A pooled analysis of 3 trials demonstrated that TNF inhibitors (adalimumab and infliximab) were significantly superior to placebo for maintenance of clinical remission (RR 2.29; 95% CI 1.73 to 3.03). There was no significant difference in clinical remission rates between the anti-TNF agents and glucocorticoid treatment (RR 1.01; 95% CI 0.73 to 1.42).

New Guidelines:

NICE

NICE updated guidelines on the management of ulcerative colitis in June 2013.¹⁴ For the most part, topical and/or oral aminosalicylates are recommended as first step therapy to induce remission in patients with mild to moderate UC. For more severe disease, IV corticosteroids and IV cyclosporin or surgery are recommended. Infliximab is recommended but the guidance is included in a separate appraisal guidance and has been reviewed previously. No other biological treatments are included in the guideline.

American Gastroenterological Association Institute

Guidelines on the use of thiopurines, methotrexate, and anti-TNF alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease were published at the end of 2013.¹⁵ Recommendations including any of the TIMs are included:

- Anti-TNF alpha drugs are recommended to induce remission in patients with moderately severe Crohn's Disease (Strong Recommendation, Moderate quality of evidence)
 - At the time, only infliximab and adalimumab were considered. Certolizumab has not been found to be more effective than placebo in inducing remission in patients.

- Recommend using TNF alpha inhibitor monotherapy over thiopurine monotherapy to induce remission in patients who have moderately severe Crohn's Disease (Strong recommendation, Moderate quality evidence).
- Recommend using TNF alpha inhibitors over no TNF inhibitors to maintain corticosteroid- or TNF inhibitor-induced remission in patients with Crohn's Disease (Strong Recommendation, High quality evidence).

New FDA Safety Alerts:

None

NEW indications/formulations:

1. In May, 2013, golimumab was FDA approved to treat adults with moderate to severe UC.^{16,17} This new indication was based on two published phase III RCT's; both included in the systematic review described above, which found that golimumab resulted in a superior clinical response than placebo (RR 1.69; 95% CI 1.41 to 2.03), but not a statistically significant improvement in clinical remission compared to placebo (RR 1.95; 95% CI 0.81 to 4.68) in the induction phase.¹² The PURSUIT-SC was an induction trial¹⁷ and PURSUIT was a maintenance study through week 54.¹⁶
2. In September 2013, certolizumab was FDA approved for the treatment of PsA in adults based on a good quality 24-week, double-blind, placebo-controlled study comparing certolizumab with placebo (RAPID-PsA).¹⁸⁻²⁰ In June 2014, NICE published an evidence summary of certolizumab for the treatment of PsA.⁷ Effectiveness was demonstrated in RAPID-PsA, a phase II study with an initial double-blind, randomized, placebo-controlled phase to week 24, a dose-blind phase without a placebo group to week 48, and an open label phase to week 216. Participants had to have active joint disease and previous failure with at least 1 DMARD. At week 12, compared with placebo, statistically significantly more people in the groups receiving certolizumab 200mg every 2 weeks, and 400mg every 4 weeks achieved an ACR20 response (58%, 51.9%, and 24.3%, respectively; $p < 0.001$ for both dosage groups compared with placebo). Statistically significant differences were also observed between the certolizumab groups and placebo for ACR50 and ACR70 response at week 12, and continued to week 24. The most common adverse effects were diarrhea and headache. The most common infectious adverse events were nasopharyngitis and upper respiratory tract infection. Discontinuations due to adverse events were low overall. The study was not powered to detect differences in the group. Long term efficacy and safety of certolizumab in PsA remains unknown. The panel concluded that certolizumab may provide an additional treatment option to the currently available agents for PsA. The evidence compared with that for other TNF inhibitors, in addition to individual patient factors and cost should be considered. There are no head-to-head trials comparing certolizumab with other TIMS for treating PsA.
3. In October 2013, certolizumab was also FDA approved for adults with active ankylosing spondylitis based on a fair quality 24-week double-blind RCT (RAPID-axSpA).²¹ Eligible patients must have previously had an inadequate response, or been intolerant to at least one NSAID. It was placebo-controlled and double blinded to week 24, dose-blinded to week 48 and is ongoing and open-label through week 204. At week 12, a statistically significant higher proportion of patients in the certolizumab 200mg every 2 weeks and 400mg every 4 week groups achieved a clinical response compared with placebo (57.7%, 63.6%, and 38.3%, respectively; $p = 0.004$ and $p < 0.001$).
4. In September 2013, ustekinumab received FDA approval for adult patients with PsA. Approval was based on the PSUMMIT 1 trial; a phase 3, double-blind, RCT in adults with active psoriatic arthritis, and the PSUMMIT 2 trial.^{22,23}

NICE published guidance on ustekinumab for treating active psoriatic arthritis in May 2014.²⁴ The following guidance is provided:

- Ustekinumab is not recommended for treating PsA, alone or in combination with methotrexate in adults when the response to previous non-biological DMARD therapy has been inadequate.
 - The committee concluded that ustekinumab appeared to be less effective than TNF alpha inhibitors for Psoriasis Area and Severity Index (PASI) 75, and Psoriatic Arthritis Response Criteria (PsARC) response rates, particularly for the joint outcome. The committee concluded that ustekinumab could not be recommended as a cost-effective use of resources.
 - In people who have not previously received TNF inhibitors, ustekinumab was dominated (more expensive and less effective than) adalimumab.
 - Evidence from 2 RCTs demonstrates that ustekinumab is clinically effective compared with conventional management, in both TNF inhibitor-naïve and TNF inhibitor-experienced patients, but there remains some uncertainty about the long term effects of ustekinumab.

Apremilast New Drug Evaluation:

Apremilast is an inhibitor of PDE4, indicated for the treatment of adult patients with active psoriatic arthritis (PsA).²⁵

Potential off-label use: Apremilast has been studied in the treatment of ankylosing spondylitis in a small pilot study with only 38 subjects.²⁶ A small phase II dose ranging study evaluated apremilast for the treatment of plaque psoriasis, also an off-label indication.²⁷ Longer-term and larger studies are needed to fully assess the efficacy and safety of apremilast for these indications. It has also been studied for use in inflammatory rosacea²⁸ and atopic dermatitis.²⁹

Clinical Efficacy:

Approval of apremilast for PsA came primarily from 3 phase III studies, with nearly identical study designs (PALACE). Only one of these phase III studies has been published and is included in the evidence table below.³⁰ The 24 week studies enrolled subjects with active PsA who had an inadequate clinical response to DMARDs and/or biologic therapy and were randomized to apremilast 20mg twice daily, apremilast 30 mg twice daily or placebo³¹. Patients with clinically significant cardiac, endocrine, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, pregnancy, and therapeutic failure of more than 3 agents for PsA, or more than one TNF blocker were excluded. The primary outcome was the proportion of patients meeting 20% improvement in modified ACR response criteria (ACR20) at week 16. At week 16, all subjects who had not improved by 20% or more were required to enter early escape and placebo-treated subjects were re-randomized to receive apremilast 20 or 30 mg. This limits the validity of the secondary outcomes at week 24, as the majority of patients had discontinued their originally assigned treatment group after week 16. Earlier phase II studies demonstrated that treatment with both 20 mg twice per day or 40 mg once a day demonstrated efficacy compared to placebo.^{32,33}

PALACE 1 is a published fair quality trial that included patients with active PsA despite prior DMARDs and/or biologics.³⁰ Biologic-naïve patients generally showed a higher ACR20 response rate compared to biologic-experienced patients and patients with a history of biologic failure achieved the lowest response rates. Secondary measures included the Disability Index of the Health assessment Questionnaire (HAQ-DI). However, this is a less commonly used measure and there is little data defining what a clinically significant improvement is.³⁴ The study authors define a minimal clinically important difference (MCID) of ≥ 0.13 and ≥ 0.30 on the HAQ-DI compared to placebo. Patients in the apremilast 30mg twice daily group had a clinically significant change in HAQ-DI significantly more than placebo (39.8% vs. 27.3%; RR 1.5; 95% CI 1.1-2.0; NNT 7), but there was no significant difference between the 20mg twice daily group and placebo (33.7%

vs. 27.3%). Overall, patients in both the 20mg and 30mg BID groups had a significantly greater proportion of patients achieving response, as measured by the ACR20, ACR50, and ACR70 versus placebo.

The two other phase III studies are unpublished and cannot be assessed for validity and/or risk of bias. They both demonstrated a statistically significant greater proportion of patients achieving ACR20 response compared to placebo and a greater change in HAQ-DI from baseline.³¹ In general, a dose-related effect was observed with higher response rates in those on apremilast 30 mg BID compared to 20 mg BID, although statistical comparison was not conducted and we cannot conclude that the 30mg dose is superior to 20mg twice daily. Overall, greater than 80% of patients had a history of treatment with methotrexate and approximately 20% had been treated with a TNF inhibitor.

Clinical Safety:

Most common adverse events included diarrhea, nausea, headache and upper respiratory tract infection. A titration schedule is recommended to avoid gastrointestinal symptoms. Serious adverse events were similar among groups and clinically meaningful laboratory abnormalities were infrequent and comparable between apremilast and placebo. Both doses of apremilast had similar adverse event profiles. A treatment-dependent decrease in body weight was observed with a greater proportion of apremilast subjects experiencing a 5% or greater weight loss compared to placebo-treated subjects.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

- 1) Disease Activity
- 2) Physical Functioning
- 3) Quality of Life
- 4) Withdrawals due to Adverse Events

Primary Study Endpoint:

- 1) Disease Activity (ACR 20)

Ref./Study Design ^a	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
PALACE 1 ³⁰ RCT, PC, DE	1. apremilast 20mg BID	Demographics: Avg age 50 y/o, 90% white, 50% female, duration of PsA 7.4 yrs Inclusion Criteria: Active PsA despite prior treatment with DMARDs and/or biologics. Exclusion Criteria: Significant cardiac, endocrine, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, abnormal ECT, pregnant, chronic infection, malignancy, other autoimmune disease therapeutic failure of more than 3 agents for PsA, or more than 1 biologic TNF inhibitor.	168	<u>ACR20 at week 16:</u> 1. 51 (30.4%) 2. 64 (38.1%) 3. 32 (19.4%) 1 vs. 3 p=0.0166; RR 1.59 (1.06-2.4)	ARR 11% /NNT 9	<u>D/C due to adverse events:</u> 1. 10 (6%) 2. 12 (7.1%) 3. 8 (4.8%)	NS	Quality Rating: Fair Internal Validity: RoB <u>Selection:</u> Was a randomized trial, but no details on sequence generation and unknown allocation concealment. Patients similar at baseline. More biologic failures in placebo group. <u>Performance:</u> Double blinded; doses provided in a blister card containing identical appearing tablets. <u>Detection:</u> Unclear if outcome assessors blinded <u>Attrition:</u> Total attrition at 12% and similar between groups. Intent to treat Analysis Done External Validity: <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Significant exclusion criteria limit generalizability. Overall, patients had long-standing active disease and were treatment experienced. <u>Setting:</u> Multinational. Majority from centers in North America and Europe. <u>Outcomes:</u> Common outcomes used. ACR 50 and ACR 70 are considered more clinically significant than ACR 20 and are both provided. Did not assess quality of life.
	2. apremilast 30 mg BID		168	2 vs. 3 p=0.0001 RR 2.0 (1.3-2.9)	ARR 19%/ NNT 5	<u>Serious AEs:</u> 1. 8 (4.8%) 2. 9 (5.4%) 3. 7 (4.2%)	NS	
	3. placebo		168	<u>HAQ-DI ≥0.30 (clinically meaningful difference)</u> 1. 33.7% 2. 39.8% 3. 27.3% 1 vs. 3 p=NS	NS			
				2 vs. 3 p=0.0149 RR 1.46 (1.05-2.02)	ARR 13%/ NNT 7			
				<u>ACR50 at week 24:</u> 1. 24 (14.7%) 2. 32 (19.9%) 3. 7 (4.2%) 1 vs. 3 p=0.0013	ARR 10.5%/NNT 9			
				2 vs. 3 p=<0.0001	ARR 16%/ NNT 6			
		<u>ACR70 at week 24:</u> 1. 9 (5.5%) 2. 17 (10.6%) 3. 1 (0.6%) 1 vs. 3 p=0.0102	ARR 5%/ NNT 20					
		2 vs. 3 p=<0.0001	RR 10%/ NNT 10					

Vedolizumab:

Vedolizumab is an integrin receptor antagonist indicated for:

- Adults with moderately to severe active UC who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids³⁵:
 - Inducing and maintaining clinical response
 - Inducing and maintaining clinical remission
 - Improving endoscopic appearance of the mucosa
 - Achieving corticosteroid-free remission
- Adults with moderately to severely active Crohn's Disease who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids:
 - Achieving clinical response
 - Achieving clinical remission
 - Achieving corticosteroid-free remission

A 2014 Cochrane systematic review evaluated vedolizumab for induction and maintenance of remission in UC.³ RCTs comparing vedolizumab to placebo or control therapy were included in the review. Four studies, all with a low risk of bias, were identified (n=606). Pooled results demonstrated that vedolizumab was significantly superior to placebo for induction of remission, clinical response, and endoscopic remission and prevention of relapse. The authors concluded that there is moderate to high quality data from 4 studies showing that vedolizumab is superior to placebo for induction of clinical remission (77% of vedolizumab patients failed to enter clinical remission vs. 92% of placebo patients; RR 0.86; 95% CI 0.80 to 0.91) and response (48% of vedolizumab patients failed to have a clinical response compared to 72% of placebo; RR 0.68; 95% CI 0.59 to 0.78) in patients with moderate to severely active UC and prevention of relapse (RR 0.67; 95% CI 0.59 to 0.77) in patients with quiescent UC.³ Moderate quality data suggests that it is also superior for prevention of relapse and adverse events appear to be similar to placebo (79% vs. 80%; RR 0.99; 95% CI 0.93 to 1.07). More studies are needed to assess the long term efficacy and safety of vedolizumab as well as comparative trials with currently approved therapies. Results from 2 studies showed that fewer vedolizumab patients withdrew due to adverse events compared to placebo (6% vs. 11%; RR 0.55; 95% CI 0.35 to 0.87). There was also no significant difference in serious adverse events between vedolizumab patients (12%) and placebo patients (12%)(RR 1.02; 95% CI 0.73 to 1.42). The most commonly reported adverse events were headache, worsening UC, nausea, frequent bowel movements, fatigue, nasopharyngitis and abdominal pain.³

Approval for Crohn's disease was based on two studies that evaluated vedolizumab 300 mg in patients who have failed previous conventional therapy.³⁶ Induction was evaluated in both trials^{37,38}; however, evaluation of maintenance was evaluated in only one trial.³⁸ Patients were required to have had an inadequate response to, loss of response to, or intolerance of at least a immunomodulator or TIM.

Study C13007 was a study with separate induction and maintenance trials. In the induction trial, patients were randomly assigned to receive blinded vedolizumab or placebo (cohort 1) at weeks 0 and 2 (n=368).³⁸ An additional 747 patients (cohort 2) were assigned open-label vedolizumab to be eligible for the

randomization into the maintenance study. In the maintenance trial, patients who had a response to vedolizumab (cohorts 1 and 2) were randomized to placebo or vedolizumab every 4 or 8 weeks until week 52. Approximately 50% of patients had previously received therapy with a TIM. There was a significant difference in clinical remission at week 6 between vedolizumab and placebo (14.5% vs. 6.8%; p=0.02; NNT 12), but no significant difference in clinical response (31.4% vs. 25.7%; p=0.02). The effect on clinical remission at week 6 was modest at best. After 52 weeks of therapy, significantly more patients on vedolizumab every 8 weeks and every 4 weeks were in clinical remission than those on placebo (39%, 36.4%, 21.6%, respectively; p<0.001 and p=0.004 for the comparisons).

Study 13011 is a phase III placebo-controlled, double blind RCT evaluating vedolizumab versus placebo in induction therapy in patients with Crohn’s disease who had failed previous therapy.³⁷ The primary efficacy analysis was only evaluated in patients with prior TNF antagonist failure and the primary outcome was clinical remission at week 6. There was no significant difference in clinical remission at week 6 between those on vedolizumab and those on placebo (15.2% vs. 12.1%; RR 1.2, 95% CI 0.7-2.2). By week 10, this subpopulation that had failed conventional therapy had achieved an improvement in remission and improved clinical remission, suggesting that it takes longer to achieve a treatment effect. In the overall population, there was a significant difference in clinical remission between vedolizumab and placebo (19.1% vs. 12.1%; RR 1.6, 95% CI 1.0-2.5). However, because the primary outcome was not statistically significant, formal hypothesis testing was not done on secondary outcomes.

Most common adverse events included infections, nausea, vomiting, headache, upper respiratory tract infection, arthralgia, nasopharyngitis, and abdominal pain, with similar rates of serious adverse events between placebo and vedolizumab. The most commonly reported serious adverse events seemed largely related to the underlying disease process. According to the FDA analysis, a hepatotoxicity signal was observed in clinical trials and several cases of acute hepatocellular injury during the clinical development program.³⁶ Vedolizumab has a similar pharmacological mechanism as natalizumab, which also has been associated with acute hepatotoxicity. The FDA was also concerned about its potential impact on Progressive multifocal leukoencephalopathy (PML) risk.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

- 1) Disease Activity
- 2) Physical Functioning
- 3) Quality of Life
- 4) Withdrawals due to Adverse Events

Primary Study Endpoint:

- 2) Clinical remission (CDAI score of ≤150 points)
- 3) Clinical Response (≥100 point increase in CDAI score)
- 4) Maintenance of Clinical remission

Ref./Study Design ^a	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
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<p>Study C13007³⁸ RCT, DB, PC</p>	<p><i>Induction:</i> Vd 300 mg</p> <p>Placebo</p> <p>Maintenance: Vd 300 mg Q4W</p> <p>Vd300 mg Q8W placebo</p>	<p>Demographics: Mean age 36.1, 46.6% male, 89.2% white, duration of disease 9 years</p> <p>Inclusion Criteria: Adults with CDAI score of 220-450 points. Previous lack of response or side effects from steroids, immunosuppressives, or TNF inhibitors. Previous TNF inhibitor limited to 50% of total study population</p> <p>Inclusion criteria: previous treatment with natalizumab, rituximab, efalizumab .Patients with a stoma, short-bowel syndrome, abdominal abscess, active or latent TB, cancer, any unstable major medical disorder, substance abuse, active psychiatric problems, SCr > 2 x ULN, alk phos >3 x ULN, Hg<8g/dl, WBC <3 platelet count <100 x 10⁹/L</p>	<p>967 (220 blinded and 747 open-label for maintenance study)</p> <p>148</p> <p>660</p> <p>154</p> <p>301</p>	<p>Induction Study: <u>Clinical remission at week 6:</u> Vd: 32 (14.5%) Pl: 10 (6.8%) P=0.02</p> <p><u>Clinical response at week 6</u> Vd: 69 (31.4%) Pl: 38 (25.7%) P=0.23</p> <p>Maintenance Study: <u>Clinical remission at week 52:</u> VdQ8W: 60 (39.0%) VdQ4W: 56 (36.4%) Pl: 33 (21.6%) P<0.001 VdQ8 vs. Pla</p> <p>P=0.004 VdQ4 vs. Pla</p>	<p>ARR 8%/ NNT 12</p> <p>NS</p> <p>ARR 17%/ NNT 5</p> <p>ARR 15%/ NNT 6</p>	<p>Induction Study: <u>D/C due to adverse events:</u> Vd: 9 (4.1%) Pla: 7 (4.7%)</p> <p>Maintenance Study: <u>D/C due to adverse events:</u> Vd: 9 (4.1%) Pla: 7 (4.7%)</p> <p><u>Serious AEs:</u> VdQ8w: 12 (7.8%) VdQ4w: 80 (14%) Pla: 15 (9.8%)</p>	<p>NS</p> <p>NS</p> <p>NS</p>	<p>Quality Rating: Fair</p> <p>Internal Validity: RoB <u>Selection:</u> Computer generated randomization at a central location. Groups similar at baseline. <u>Performance:</u> Double Blinded <u>Detection:</u> Unclear <u>Attrition:</u> Low attrition in induction study, but high attrition in maintenance study (approximately 50%)</p> <p>External Validity: <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Significant exclusion criteria reduces generalizability of results <u>Setting:</u> Multinational. <u>Outcomes:</u> Common Clinical outcomes evaluated</p>
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Study 13011 RCT, DB, PC ³⁷	<p><i>Prior TNF failure:</i></p> <p>Vd 300mg Placebo</p> <p><i>TNF naïve:</i></p> <p>Vd 300mg Placebo</p>	<p>Demographics: Mean age 34.8, 57% female, median disease duration 8 years, prior TIM failure 76%</p> <p>Inclusions Criteria: Adults with Crohn's disease with an inadequate response, loss of response, or intolerance to TNF antagonists, immunosuppressives, or corticosteroids.</p> <p>Exclusion criteria: Unstable or uncontrolled medical condition, neurologic disorder, malignancy, drug or alcohol dependence, psychiatric disease.</p>	<p>158 157</p> <p>51 50</p>	<p><u>Clinical Remission at week 6 (TNF failure):</u> Vd: 15.2% Pla: 12.1% P=0.433 RR 1.2; 95% CI 0.7-2.2</p> <p>*Official hypothesis testing not done on secondary endpoints since primary outcome was not statistically significant</p>	NS	<p><u>D/C due to adverse events:</u> Vd: 4 (2%) Pla: 8 (4%)</p> <p><u>Serious adverse events:</u> Vd: 13 (6%) Pla: 16 (8%)</p>	NS NS	<p>Quality Rating: Fair</p> <p>Internal Validity: RoB <u>Selection:</u> Randomized using a interactive voice response system and computer-generated randomization sequence. <u>Performance:</u> Double Blinded using sale bag covers and labels. <u>Detection:</u> Unclear blinding of outcome assessors. <u>Attrition:</u> Low attrition (4%) but short term study. Similar between groups. Intent to treat analysis done for primary outcome.</p> <p>External Validity: <u>Recruitment:</u> Unclear <u>Patient Characteristics:</u> Significant exclusion criteria reduces generalizability of results <u>Setting:</u> Multinational. <u>Outcomes:</u> Common Clinical outcomes evaluated. Only evaluating induction therapy; unknown long term maintenance of remission in patients.</p> <p>Efficacy analysis conducted in subgroup of patients.</p>
CDAI: Crohn's Disease Activity Index								

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Appendix 1: Suggested PA Criteria

Biologicals for RA, Psoriasis, or Crohn's Disease

Goal(s):

- Cover biologicals according to OHP list guidelines.
- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products.

Requires PA: Non-preferred products

Preferred Products: Adalimumab (Humira®), Etanercept (Enbrel®),

Length of Authorization: 12 months

Generic Name	Trade Name	Indication
Abatacept	Orencia	RA, Juvenile RA, Juvenile idiopathic arthritis
Adalimumab	Humira	RA, Psoriatic arthritis, ankylosing spondylitis, Juvenile idiopathic arthritis, Crohn's disease, Plaque psoriasis, ulcerative colitis
Anakinra	Kineret	RA
Apremilast	Otezla	Psoriatic arthritis, plaque psoriasis
Certolizumab	Cimzia	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis
Etanercept	Enbrel	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis
Golimumab	Simponi	RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Infliximab*	Remicade	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis
Natalizumab*	Tysabri	Crohn's disease, Multiple Sclerosis
Rituximab*	Rituxan	RA, CLL, Wegener granulomatosis, Microscopic polyangiitis, Non-Hodgkin lymphoma
Tocilizumab*	Actemra	RA, juvenile idiopathic arthritis
Ustekinumab	Stelara	Plaque psoriasis, psoriatic arthritis
Tofacitinib	Xeljanz	RA
Vedolizumab	Entyvio	Ulcerative colitis, Crohn's disease

Abbreviations: RA, rheumatoid arthritis; CLL: Chronic Lymphocytic Leukemia

* Must be billed via J-code and payment requires trial of preferred self-administered drug first.

Author: M. Herink, Pharm.D.

Approval Criteria : Biologicals

1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis covered by OHP?	Yes: Go to #3	No: Pass to RPH; Deny (medical appropriateness)
3. Will the provider change to a preferred product?	Yes: Inform provider of covered alternatives in class.	No: Go to #4
4. Is the diagnosis psoriasis (ICD-9: 696.1-696.2, 696.8) and the product requested FDA approved for psoriasis (see table above)? * Moderate/Severe psoriasis treatments are covered on the OHP.	Yes: Refer to anti-psoriatics PA criteria at http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/OR%20Medicaid%20PA%20Criteria/PA%200711.pdf	No: Go to #5
5. Is the diagnosis ankylosing spondylitis (ICD-9 720) and the product requested is FDA approved for ankylosing spondylitis?	Yes: Approve treatment for up to 1 year	No: Go to #6
6. Is the diagnosis rheumatoid arthritis (ICD-9 714.xx) or psoriatic arthropathy (ICD-9 696.0) and the product requested FDA approved for rheumatoid arthritis (see table above)?	Yes: Go to #7	No: Go to #8
7. Has the patient had a trial and inadequate response to methotrexate or other first line DMARDs (leflunomide, sulfasalazine, hydroxychloroquine, penicillamine) and a disease duration of ≥6 months? Or, An intolerance or contraindication to oral DMARDs?	Yes: Approve treatment for up to 1 year	No: Pass to RPH; Deny (medical appropriateness)
8. Is the diagnosis Crohn's disease (ICD-9 555) and the product requested FDA approved for Crohn's (see table above)?	Yes: Go to #9	No: Pass to RPH; Deny (medical appropriateness)
9. Has the patient had a trial and inadequate response to conventional therapy including immunosuppressive therapy (mercaptopurine, azathioprine) and/or corticosteroid treatments? Or, Has intolerance or contraindications to conventional therapy?	Yes: Approve treatment for up to 1 year	No: Pass to RPH; Deny (medical appropriateness)

P&T Action: 8-30-12 (MH)

Revision(s):

Initiated:

