Drug Use Research & Management Program
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Conclusions and Recommendations: Targeted Immune Modulators (TIMS)

Current Status of PDL Class:

- Preferred Agents: ADALIMUMAB (HUMIRA®), ETANERCEPT (ENBREL®), INFLIXIMAB (REMICADE®)
- Non Preferred: ABATACEPT (ORENCIA®), ALEFACEPT (AMEVIVE®), ANAKINRA (KINERET®), CERTOLIZUMAB (CIMZIA®), EFALIZUMAB (RAPTIVA®), NATALIZUMAB (TYSABRI®), RITUXIMAB (RITUXAN®)
- Prior authorization is required for non-preferred PDL drugs to ensure that non-preferred drugs are used for an above-the-line condition.

Research Questions:

- Does any of the new information from the Drug Effectiveness Review Project (DERP) class update[1] or clinical guidelines change previous conclusions regarding effectiveness, safety, and current management of TIMs?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

Conclusions:

- Three new TIMs were approved and included in the third DERP update. Golimumab (Simponi®) is a tumor necrosis factor (TNF) inhibitor FDA approved for rheumatoid arthritis, psoriatric arthritis, and ankylosing spondylitis. Tocilizumab (Actemra®) is an interleukin (IL)-6 monoclonal antibody approved for rheumatoid arthritis and juvenile idiopathic arthritis. Ustekinumab (Stelara®) is an IL-12 and IL-23 monoclonal antibody FDA approved for plaque psoriasis.
- For the treatment of rheumatoid arthritis (RA), there is low strength evidence that abatacept is more effective than infliximab in patients with an inadequate response to methotrexate at 1 year (1 fair quality head to head trial), although infliximab was administered at a fixed dose.[1]
- For the treatment of RA, there is low strength evidence that there is no difference between adalimumab and etanercept and that adalimumab and etanercept are more efficacious than infliximab.[1]
- For the treatment of RA, the majority of studies enrolled patients who had failed at least one disease-modifying antirheumatic drug (DMARD) treatment or were on a stable dose of methotrexate (MTX) with unsatisfactory response.
- The American College of Rheumatology recently updated their recommendations (2012) for biologic agents in treating RA and recommend starting an anti-TNF medication with or without methotrexate only in RA with high disease severity and features of poor prognosis (after 3 months of methotrexate monotherapy or DMARD combination therapy) with the level of evidence A for infliximab with methotrexate and B for etanercept, adalimumab, golimumab, and certolizumab with or without methotrexate.[2]
- There is no evidence on the comparative effectiveness of TIMS for treatment of juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, or crohns disease.[1]

- Studies included patients who had disease despite treatment with corticosteroids and methotrexate in juvenile idiopathic arthritis, and DMARD failure for plaque psoriasis.
- Only infliximab is currently approved for the treatment of ulcerative colitis.
- There is low quality evidence based on one 16 week head-to-head trial that ustekinumab produced a significantly better response than etanercept in patients with plaque psoriasis (67.5-73.8% vs. 56.8%, p<0.001).[1]

Recommendations:

- Maintain the most recently approved TIMS, golimumab, tocilizumab, and ustekinumab as non-preferred TIMS due to limited comparative evidence and lack of clinical benefit compared to currently available TIMS.
- Based on new clinical evidence, recommend no changes to current preferred TIMS on the PDL.
- Consider additional clinical criteria for prior authorization of non-preferred TIMS including a step therapy requirement with a trial of methotrexate first for RA and limited to the appropriate FDA indications for each non-preferred drug.
- Consider a DUE to evaluate preferred products for off-label use or use inconsistent with current clinical guidelines.

Guidelines:

The American College of Rheumatology published 2012 revised updates in select topic areas.[2] This update separates recommendations for early and established RA which are defined as disease duration < 6 months and > 6 months, respectively. For early RA, the guidelines recommend DMARD monotherapy initially and the use of an anti-TNF biologics with or without MTX only in patients who have high disease activity and with poor prognostic features.[2] They designated a level of evidence A for infliximab in combination with MTX, and level of evidence B for etanercept, adalimumab, golimumab, and certolizumab with or without MTX. In established RA, the panel recommends DMARD monotherapy and combination therapy before switching to an anti-TNF biologic.[2] IF a patient has moderate or high disease activity after 3 months of methotrexate monotherapy or DMARD combination therapy, an alternative is switching to an anti-TNF biologic, or to abatacept or rituximab in TNF-naïve patients. This included level of evidence A for etanercept, infliximab, adalimumab, golimumab, certolizumab, abatacept, and rituximab all in combination with MTX. These same agents are given a level of evidence C when given without MTX.[2]

The national clinical guidelines on the management of early RA from the Scottish Intercollegiate Guidelines Network (SIGN) from 2011 state that the use of the TNF inhibitors for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate or other DMARDs is not recommended.[3] Clinical guidelines from the National Institute for Clinical Excellence (NICE) recommend that adalimumab, etanercept, and infliximab are options for adults with active RA and for those who have undergone trials of two DMARDS, including MTX (defined as 6 months).[4]

For the treatment of juvenile idiopathic arthritis, the American College of Rheumatology recommends the initiation of TNF-inhibitors in patients who have received glucocorticoid joint injections and 3 months of MTX at the maximum tolerated dose (level of evidence C).[5] For systematic arthritis, level C evidence supports the initiation of anakinra in all patients with active fever and features of poor prognosis.

References:

1. Thaler K, Gartlehner G, Kien C, et al. Drug class review: Targeted immune modulators. Final update 3 report. 2012. Available at: http://www.ohsu.edu/drugeffectiveness/reports/final.cfm.

2. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2012;64(5):625–639.

3. Scottish Intercollegiate Guidelines Network (SIGN). Management of early rhematoid arthritis. A national clinical guideine. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN). 2011;(SIGN publication; no. 123):27 p.

4. National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: the management of rheumatoid arthritis in adults. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Feb. 35 p. (NICE clinical guideline; no. 79).

5. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res (Hoboken).* 2011;63(4):465–482.