Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Use Evaluation: Preferred Targeted Immune Modulators (TIMs)

A drug class review on Targeted Immune Modulators (TIMs) was conducted and discussed during the June P&T committee.[1] The goal of this evaluation is to assess the off-label use, recommended dosage and safety concerns of the preferred drugs, which include adalimumab, etanercept, and infliximab.

Background:

Adalimumab, administered by subcutaneous injection, is Food and Drug Administration (FDA) approved for rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), and plaque psoriasis (Ps).[2] In addition, it is used for the treatment of ulcerative colitis (UC) off-label.[3,4] Table 1 lists the FDA recommended doses for adalimumab. The use of adalimumab beyond one- year for the treatment of CD and PP has not been evaluated in clinical trials, therefore long-term safety and efficacy for these indications is not known. The FDA recommends careful monitoring of patients taking adalimumab with a history of congestive heart failure (CHF), previous diagnoses with hepatitis B, tuberculosis, and Central Nervous System (CNS) demyelinating disease (multiple sclerosis, optic neuritis, Guillain-Barre syndrome). Higher incidences of infection and malignancy have been reported in the elderly taking adalimumab compared to younger adults.

Table 1-FDA approved indications and dosages for adalimumab

Indication	Recommended Dose Range	Maximum Recommended Dose
RA - Rheumatoid arthritis	40mg every other week	40mg every week (without concurrent MTX)
JIA - Juvenile idiopathic arthritis (age 4-17)	15kg (33lbs) to <30kg (66 lbs): 20 mg every other week ≥30kg (66lbs): 40mg every other week	
PsA - Psoriatic arthritis	40mg every other week	40mg every week (without concurrent MTX)
AS - Ankylosing spondylitis	40mg every other week	40mg every week (without concurrent MTX)
CD - Crohn's disease	Initial dose (Day 1)160mg; On Day 15 80mg; Maintenance begins on Day 29 at 40mg every other week	
Ps - Plaque psoriasis	80mg initial dose, then 40mg every other week starting one week after initial dose	

MTX = methotrexate

Etanercept is FDA approved for the treatment of RA, polyarticular JIA in patients age ≥2 years, PsA, and Ps.[5] Etanercept has also been used to treat scleroderma, Alzheimer's disease, and Wegener's granulomatosis off-label.[6–8] The FDA does not recommend the use of etanercept in patients with Wegener's granulomatosis who are also receiving immunosuppressive treatment. Table 2 lists the FDA approved doses for etanercept. Caution should be taken in patients with a history of hepatitis B virus, tuberculosis, congested heart failure (CHF), demyelinating CNS disease, and moderate to severe alcoholic hepatitis. In addition, hypoglycemia following initiation of etanercept in patients receiving diabetic medications has been reported, therefore patients taking diabetic medications should be monitored and dose adjusted if needed. No overall difference in safety or effectiveness among geriatrics was observed in comparison to younger patients.

Table 2-FDA approved indications and dosages for etanercept

Indication	**Recommended Dose Range**	**Maximum Recommended Dose**
RA	50mg once weekly with or without MTX	
Polyarticular JIA (≥2 years of age)	0.8mg/kg weekly	50mg/week
PsA	50mg once weekly with or without MTX	
AS	50mg once weekly	
Ps	50mg twice weekly for 3 months, followed by 50mg once weekly	

The FDA approved indications for infliximab include pediatric and adult Wegener's granulomatosis, CD, pediatric and adult UC, RA in combination with MTX, AS, PsA, and Ps.[9] Infliximab is used off-label in the treatment of Behcet's Disease and age-related macular degeneration.[10–12] Table 3 lists the FDA approved doses for infliximab. Pediatric CD and UC are only indicated for children older than six years old due to the lack of studies in younger children. Like the other TIMs, infliximab should be used with caution in patients with demyelinating disease, hepatitis B, tuberculosis, seizure disorders, and heart failure. Patients with moderate to severe heart failure (NYHA Class III/IV) should not be dosed with >5mg/kg of infliximab due to risk of heart failure exacerbation. Geriatrics may have a higher incidence of infection.[9]

All of the preferred medications have an FDA warning for severe and possibly fatal infections related to their use. Due to these findings, their use is contraindicated in patients with active acute hepatitis B or C, tuberculosis, herpes zoster, fungal or bacterial infections.

Table 3-FDA approved indications and dosages for infliximab

Indication	Recommended Dose/Dose Range	Maximum Recommended Dose
CD	5mg/kg at 0, 2, 6 weeks, then every 8 weeks	10mg/kg if they later lose response
Pediatric CD	5mg/kg at 0, 2, 6 weeks, then every 8 weeks	
UC	5mg/kg at 0, 2, 6 weeks, then every 8 weeks	
Pediatric UC	5mg/kg at 0, 2, 6 weeks, then every 8 weeks	
RA (with MTX)	3mg/kg at 0, 2, 6 weeks, then every 8 weeks	10mg/kg or treat every 4 weeks if needed
AS	5mg/kg at 0, 2, 6 weeks, then every 6 weeks	
PsA	5mg/kg at 0,2, 6 weeks, then every 8 weeks	
Ps	5mg/kg at 0,2, 6 weeks, then every 8 weeks	

In 2012, the American College of Rheumatology published revised treatment guidelines.[13] This update separates recommendations for early (<6 months) and established (> 6 months) RA. For early RA, the guidelines recommend DMARD monotherapy initially and the use of TIMs with or without MTX only in patients who have high disease activity and with poor prognostic features.[13] The use of infliximab in combination with MTX was designated a level of evidence A, and use of etanercept, adalimumab, golimumab, and certolizumab with or without MTX were given a level of evidence B. In established RA, the guidelines recommend DMARD monotherapy and combination therapy before switching to a TIM.[13] Patients must undergo a 3 month trial with MTX monotherapy or DMARD combination therapy. If moderate or high disease activity persists after 3 months, an alternative is switching to a TIM. 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.[13]

The 2011 national clinical guidelines on the management of early RA from the Scottish Intercollegiate Guidelines Network (SIGN) state that the use of the TIMs for the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs is not recommended.[14] Clinical guidelines from the National Institute for Clinical Excellence (NICE) in 2009 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 (for 6 months).[15]

The American College of Rheumatology recommends the initiation of TIMs in patients with JIA who have received glucocorticoid joint injections and 3 months of MTX at the maximum tolerated dose (level of evidence C).[16] For systematic arthritis, level C evidence supports the initiation of anakinra in all patents with active fever and features of poor prognosis.

The SIGN guidelines for psoriasis and PsA recommend NSAIDs for short term symptom relief.[17] The use of DMARDs (leflunomide, sulfasalazine, or MTX) for the treatment of PsA is recommended first line. TIMs are only recommended after failed responses to two different DMARD therapies, each treated for at least a 3 month period.

The guidelines of care for the management of psoriasis and PsA from the Journal of the American Academy of Dermatology were updated in 2009.[18] They recommend that topical agents such as corticosteroids and vitamin D analogues or systemic agents such as MTX and cyclosporine should be used as first line depending on severity of the Ps. Only when trial periods with these agents have failed can patients be recommended to use TIMs.

In 2008, NICE guidelines issued recommendations for biologic therapy use in AS. The recommendations state that adalimumab and etanercept may be considered as possible treatments for people with severe AS who have tried at least two non-steroidal anti-inflammatory drugs (NSAIDs) but failed to work. [19]

The American College of Gastroenterology (ACG) and the Gut Guidelines both recommend that patients with CD or UC first be unsuccessfully treated with aminosalicylates, corticosteroids and immunomodulators before a TIM is administered.[20-22]

Treatment Guidelines are summarized in Table 4.

Table 4 – Treatment Guidelines

Disease	Guidelines	Recommendations
RA	American College of Rheumatology (2012)[13] Scottish Intercollegiate Guidelines Network (2011)[14] National Institute for Clinical Excellence (2009)[15]	Early RA (<6 mo)=DMARD monotherapy initially, then biologics with or without MTX Established RA (>6 mo)=DMARD monotherapy and combination therapy before starting biologics (DMARD for 3-6 months depending on guidelines)
JIA	American College of Rheumatology (2011)[16]	Glucocorticoid joint injections and 3 months of MTX before initiating biologics
PsA	Scottish Intercollegiate Guidelines Network (2010)[17]	NSAIDS for short term relief; DMARD therapy for 3 months before starting biologics
Ps	Journal of the American Academy of Dermatology (2009)[18]	Corticosteroids, vitamin D analogues or systemic agents (MTX and cyclosporine) should be used as first line depending on severity; if failed, biologics can be used
AS	National Institute for Clinical Excellence (2008)[19]	Adalimumab and etanercept may be considered after trying at least two non-steroidal anti-inflammatory drugs (NSAIDs)
CD	The American College of Gastroenterology (2010)[20,21] Gut Guidelines (2004)[22]	Unsuccessfully treated with aminosalicylates, corticosteroids and immunomodulators before biologics can be started
UC	The American College of Gastroenterology (2010)[20,21] Gut Guidelines (2004)[22]	Unsuccessfully treated with aminosalicylates, corticosteroids and immunomodulators before biologics can be started

Methods

Patients were selected for inclusion if they had a new fee-for-service (FFS) pharmacy or professional claim for any of the preferred drugs during 2011. See appendix A for a list of codes used to identify the preferred drugs. The definition of "new" was a patient with no prior history of any TIMs use (FFS or managed care) in the year prior to the index claim. See Appendix B for list of codes to identify TIMs drugs. Patients needed to be continuously eligible for at least 75% of the year prior and 100% eligible 90 days before and after the index claim. Only patients with valid demographic data and without Medicare Part D coverage were included. Recommended and maximum doses are defined in Appendix A. The "Days Supply" field was used for pharmacy

claims to calculate a daily dose (Quantity Dispensed x Strength per Unit divided by the Days Supply). For professional claims the days between fills were determined as a proxy for Days Supply and calculated similarly. Concurrent DMARD therapy was determined for all patients on a preferred product for a minimum of 60 day spans (7 day gap allowed). A minimum of 30 days of overlap was considered concurrent therapy. Codes to identify DMARDs are in Appendix C. Finally, International Classification of Diseases, 9th Revision (ICD-9) diagnostic codes was identified in the year prior to the index fill to associate potential uses for the TIMs and co-morbid conditions. These are listed in Appendix D.

Results

There were a total of 42 new patients identified using a preferred TIMs (Table 5). A majority of the patients were adult white females between the ages of 19-65 years. None of the patients were below the age restriction for the specific TIM used.

Table 5-Demographics of all users

	All Users	
Total	42	(%)
Age		
Mean	47.3	
Range	7-93	
<6	0	0.0%
6-12	2	4.8%
13-18	1	2.4%
19-65	31	73.8%
>65	8	19.0%
Female	26	61.9%
Race		
White	37	88.1%
Hispanic	0	0.0%
American Indian	2	4.8%
Black	2	4.8%
Asian	0	0.0%
Other	1	2.4%

Table 6 lists the preferred drugs and numbers of patients taking each of them. The most commonly used TIM was infliximab followed by adalimumab and then etanercept.

Table 6-Distribution of all users

Drug	N= 42	(%)
ADALIMUMAB	12	28.57%
ETANERCEPT	6	14.29%
INFLIXIMAB	24	57.14%

The average daily doses prescribed for each drug were reviewed. The results show that infliximab had the highest occurrence of patients exceeding the maximum recommended dose per day (Table 7 and 8) at a rate of 50% of the included patients on infliximab. All of the prescribed TIMs had incidences of doses exceeding the maximum recommendation.

Table 7 - Dose Analysis of users (pharmacy users only)

Drug	N=	Avg Daily Dose (mg)	Patients exceeding maximum recommended dose/ day	(%) of patients on drug
ADALIMUMAB	12	3.3	3	25%
ETANERCEPT	6	6.7	2	33%
INFLIXIMAB	0	-	0	-

Table 8 - Dose Analysis of Users (professional claims only)

Drug	N=	Avg Daily Dose (mg)	Patients exceeding maximum recommended dose/ day	(%) of patients on drug
INFLIXIMAB (J1745)	18	11.4	9	50%

Note: The "N" is the count of patients with adequate dosage information to determine an average for that patient. It is not a comprehensive count of all patients on that drug.

Data was queried for the prevalence of concurrent DMARD use in patients taking TIMs, but no concurrent use of medications was found.

Table 9 categorizes each of the TIMs using the FDA approved indications to determine the most commonly used disease state in which they are prescribed. The preferred TIMs are most commonly associated with RA, though infliximab is also highly associated with CD. There were eight (16.3%) patients with no history of an FDA approved diagnosis for the TIMs.

Table 9 - FDA approved diagnostic information for users by drug in year prior to index drug (patients may be in >1 diagnostic group)

Drug	N=	RA	JIA	PsA	Ps	AS	CD	UC	No FDA Dx	Any FDA Dx
ADALIMUMAB	12	3		4	1	1			4	8
ETANERCEPT	6	1		2	2				3	3
INFLIXIMAB	24	8		1	1	4	8	3	1	23

Off-label uses for the preferred TIMs were evaluated and none of the patients had a diagnosis of the specified off-label indications. Cautionary diagnostic information was also queried from the year prior to the use of the drugs and four of 42 patients (9.5%) were identified. Adalimumab had one patient with a diagnosis of seizure and one with an infection diagnosis. Etanercept had one diagnosis of heart failure and infliximab had one diagnosis of multiple

sclerosis. Incidence of infection 90 days after the start of TIMs was evaluated and only one occurrence of infection was documented which included a diagnosis hepatitis C in a patient taking adalimumab.

DMARDs, which are the first line therapy for RA, PsA and an optional first line for Ps, were used in seven patients 1 year prior to the initiation of TIMs (Table 10).

Table 10-Users with DMARD in 1 year previously

Drug	**N= 42**	**%**
ADALIMUMAB	5	11.9%
ETANERCEPT	2	4.8%
INFLIXIMAB	0	0.0%

Discussion

This analysis is limited because it uses retrospective administrative data and thus suffers from the possibility of missing diagnostic information. Diagnostic information cannot be directly linked to drug use but is associated by patient and time period only. This evaluation is not controlled and merely descriptive. Finally, the sample size is very small with only 42 new patients identified. Thus conclusions should be cautiously drawn and applied to the larger population.

There was no evidence of use for identified off-label indications or for children under the recommended age. The recommended dose was exceeded in 25-50% of patients. Four patients (9.5%) with a past history of seizure, MS, or infection were identified which are contraindicated conditions in the use of some TIMs. Of most concern is the low number of patients where previous DMARD therapy was detected in the year before the index TIMs claim. It appears TIMs are not used in accordance with treatment guidelines.

Recommendations

1. Consider prior authorization to ensure DMARDs are used first line
2. Initiate a quantity limit to prevent doses from exceeding recommendations

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. Abbott Laboratories.Abbott Park, IL 60064. Prescribing information for Humira®. 2012.
3. Warner B, Harris AW. Adalimumab Induces and Maintains Clinical Remission in Patients With Moderate-to-Severe Ulcerative Colitis. *Gastroenterology*. 2012;143(1):e42.
4. Danese S. Adalimumab in ulcerative colitis: Ready for prime time. *Digestive and Liver Disease*. (0). Available at: http://www.sciencedirect.com/science/article/pii/S1590865812002046. Accessed July 27, 2012.
5. Amgen Inc.Thousand Oaks, CA 91320. Prescribing information for Enbrel®. 2011.
6. Koca SS, Isik A, Ozercan IH, Ustundag B, Evren B, Metin K. Effectiveness of etanercept in bleomycin-induced experimental scleroderma. *Rheumatology (Oxford)*. 2008;47(2):172–175.
7. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N. Engl. J. Med.* 2005;352(4):351–361.
8. Tobinick E. Deciphering the physiology underlying the rapid clinical effects of perispinal etanercept in Alzheimer's disease. *Curr Alzheimer Res*. 2012;9(1):99–109.
9. Janssen Biotech. Horsham, PA 19044. Prescribing information for Remicade®. 2012.
10. Okada AA, Goto H, Ohno S, Mochizuki M. Multicenter study of infliximab for refractory uveoretinitis in Behçet disease. *Arch. Ophthalmol.* 2012;130(5):592–598.
11. Arias L, Caminal JM, Badia MB, Rubio MJ, Catala J, Pujol O. Intravitreal infliximab in patients with macular degeneration who are nonresponders to antivascular endothelial growth factor therapy. *Retina (Philadelphia, Pa.)*. 2010;30(10):1601–1608.
12. Theodossiadis PG, Liarakos VS, Sfikakis PP, Vergados IA, Theodossiadis GP. Intravitreal administration of the anti-tumor necrosis factor agent infliximab for neovascular age-related macular degeneration. *Am. J. Ophthalmol.* 2009;147(5):825–830, 830.e1.
13. 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.
14. 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.
15. 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).
16. 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.

Appendix A – Codes identifying preferred drugs in fee-for-service pharmacy and professional claims

GSN	Drug	Drug Strength per Billing Unit	Maximum recommended billing units per day	Corresponding Recommended Dose
51599	ADALIMUMAB	40	0.071	40 mg every other week
61205	ADALIMUMAB	40	0.071	40 mg every other week
63724	ADALIMUMAB	20	0.143	40 mg every other week
40869	ETANERCEPT	25	0.286	50mg once weekly
58214	ETANERCEPT	50	0.143	50mg once weekly
61938	ETANERCEPT	50	0.143	50mg once weekly
62624	ETANERCEPT	50	0.143	50mg once weekly
40650	INFLIXIMAB	100	0.119	100kg (at 5mg/kg) every 6 weeks
J0135	ADALIMUMAB	20	0.143	40 mg every other week
J1438	ETANERCEPT	25	0.286	50mg once weekly
J1745	INFLIXIMAB	10	1.190	100kg (at 5mg/kg) every 6 weeks

Appendix B – Codes identifying TIMs drugs in fee-for-service or managed care pharmacy or professional claims

GSN/ J-code	Drug
67681	ABATACEPT
J0129	Abatacept injection
60226	ABATACEPT/MALTOSE
51599	ADALIMUMAB
61205	ADALIMUMAB
63724	ADALIMUMAB
J0135	ADALIMUMAB
51694	ALEFACEPT
51695	ALEFACEPT
J0215	Alefacept
48899	ANAKINRA
63903	CERTOLIZUMAB PEGOL
65189	CERTOLIZUMAB PEGOL
J0718	Certolizumab pegol inj
40869	ETANERCEPT
58214	ETANERCEPT
61938	ETANERCEPT
62624	ETANERCEPT
J1438	ETANERCEPT
65113	GOLIMUMAB
65114	GOLIMUMAB
40650	INFLIXIMAB
J1745	INFLIXIMAB
58384	NATALIZUMAB
J2323	Natalizumab injection
65775	OFATUMUMAB
67553	OFATUMUMAB
J9302	Ofatumumab injection
63759	RILONACEPT
36870	RITUXIMAB
J9310	Rituximab injection
65409	TOCILIZUMAB
65410	TOCILIZUMAB
65411	TOCILIZUMAB
J3262	Tocilizumab injection
65993	USTEKINUMAB
65994	USTEKINUMAB
J3357	Ustekinumab injection

Appendix C – Codes identifying DMARD drugs in fee-for-service or managed care pharmacy or professional claims

GSN/Jcode	GroupByCategory*	Strength
9580	HYDROXYCHLOROQUINE SULFATE	200 mg
40549	LEFLUNOMIDE	10 mg
40550	LEFLUNOMIDE	20 mg
45266	METHOTREXATE SODIUM	2.5 mg
35928	METHOTREXATE SODIUM	10 mg
36872	METHOTREXATE SODIUM	2.5 mg
36874	METHOTREXATE SODIUM	7.5 mg
47823	METHOTREXATE SODIUM	5 mg
47824	METHOTREXATE SODIUM	15 mg
42778	MINOCYCLINE HCL	75 mg
52057	MINOCYCLINE HCL	75 mg
60730	MINOCYCLINE HCL	45 mg
60731	MINOCYCLINE HCL	90 mg
60732	MINOCYCLINE HCL	135 mg
65433	MINOCYCLINE HCL	65 mg
65434	MINOCYCLINE HCL	115 mg
66683	MINOCYCLINE HCL	55 mg
66684	MINOCYCLINE HCL	80 mg
66685	MINOCYCLINE HCL	105 mg
9226	MINOCYCLINE HCL	100 mg
9227	MINOCYCLINE HCL	50 mg
9230	MINOCYCLINE HCL	100 mg
9231	MINOCYCLINE HCL	50 mg
9402	SULFASALAZINE	500 mg
9403	SULFASALAZINE	500 mg
J9250	Methotrexate sodium inj	5 MG
J9260	Methotrexate sodium inj	50 MG
J8610	Methotrexate oral 2.5 MG	2.5 MG

Appendix D – International Classification of Diseases, 9th Revision (ICD-9) diagnostic codes identified in FFS and managed care professional claims the year prior to index fill.

FDA Indications	FDA codes
Rheumatoid Arthritis (RA)	714.0
juvenile idiopathic arthritis (JIA)	714.3
Psoriatic arthritis (PsA)	696.0
Plaque Psoriasis (Ps)	696.1
Ankylosing Spondylitis (AS)	720.0
Chrohn's Disease (CD)	555.x
Ulcerative Colitis (UC)	556.x

Off-Label Indications	Off-Label Codes
Circumscribed scleroderma	701
Wegener's granulomatosis	446.4
Alzheimer's disease	331
Behcet's disease	136.1
Behcet's disease	711.2x
age-related macular degeneration	362.5

Other Infection Indications	Infection Codes
Endemic Mycoses	114.xx - 116.xx
Septic Arthritis	711.0
Listeriosis	027.0
Legionella pneumonia	482.8, 482.84
herpes zoster infection	053.xx
Cryptococcosis	117.5
Aspergillosis	117.3
Pneumocystis pneumonia	136.3
Non-healed infected skin ulcers	707.xx
Hepatitis C	070.70
Hepatitis C	070.4
Hepatitis C	070.5

Cautionary Indications	Cautionary Codes
Heart Failure	428.xx
Multiple Sclerosis	340.xx
Optic neuritis	377.3x
Guillain-Barre	357.0x
Hepatitis B	070.2x
Tuberculosis	010.xx - 018.xx
Seizure	345.xx