SPRB™

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Assessing the Evolving Value of **Rheumatoid Arthritis** Therapies

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MEDICAL EDUCATION RESOURCES

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AMCP Academy of Managed Care Pharmacy®

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Educational Objectives

- Assess decision support tools to enhance medical and pharmacy benefit design decision-making for patients with RA
- Interpret results of decision support tools with health plan affiliated rheumatology professionals to improve outcomes for patients with RA
- Employ specialty pharmacy and disease management services that can improve the quality of care for patients with RA
- Provide accurate and appropriate counsel as part of the managed care treatment team

Assessing the Clinical Benefits of Rheumatoid Arthritis Therapies in a Managed Care Setting

Robin K. Dore, MD
Clinical Professor
UCLA David Geffen School of Medicine
Los Angeles, CA

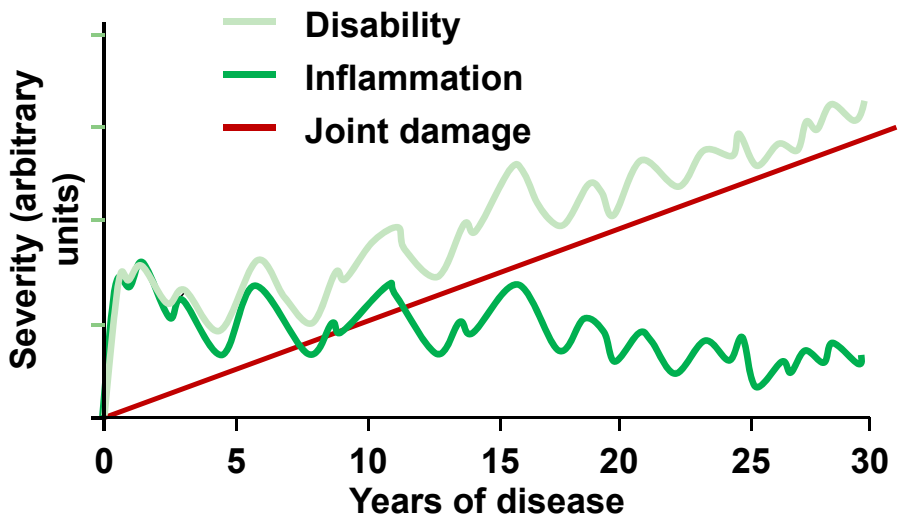
Learning Objective

- Review the clinical benefits of early and aggressive treatment of rheumatoid arthritis (RA)

RA Treatment Challenges

- Complex, multifactorial pathogenesis
- Fluctuating clinical course; unpredictable prognosis
- Characterized by
  - Progressive joint destruction
  - Loss of physical function
  - Poor quality of life

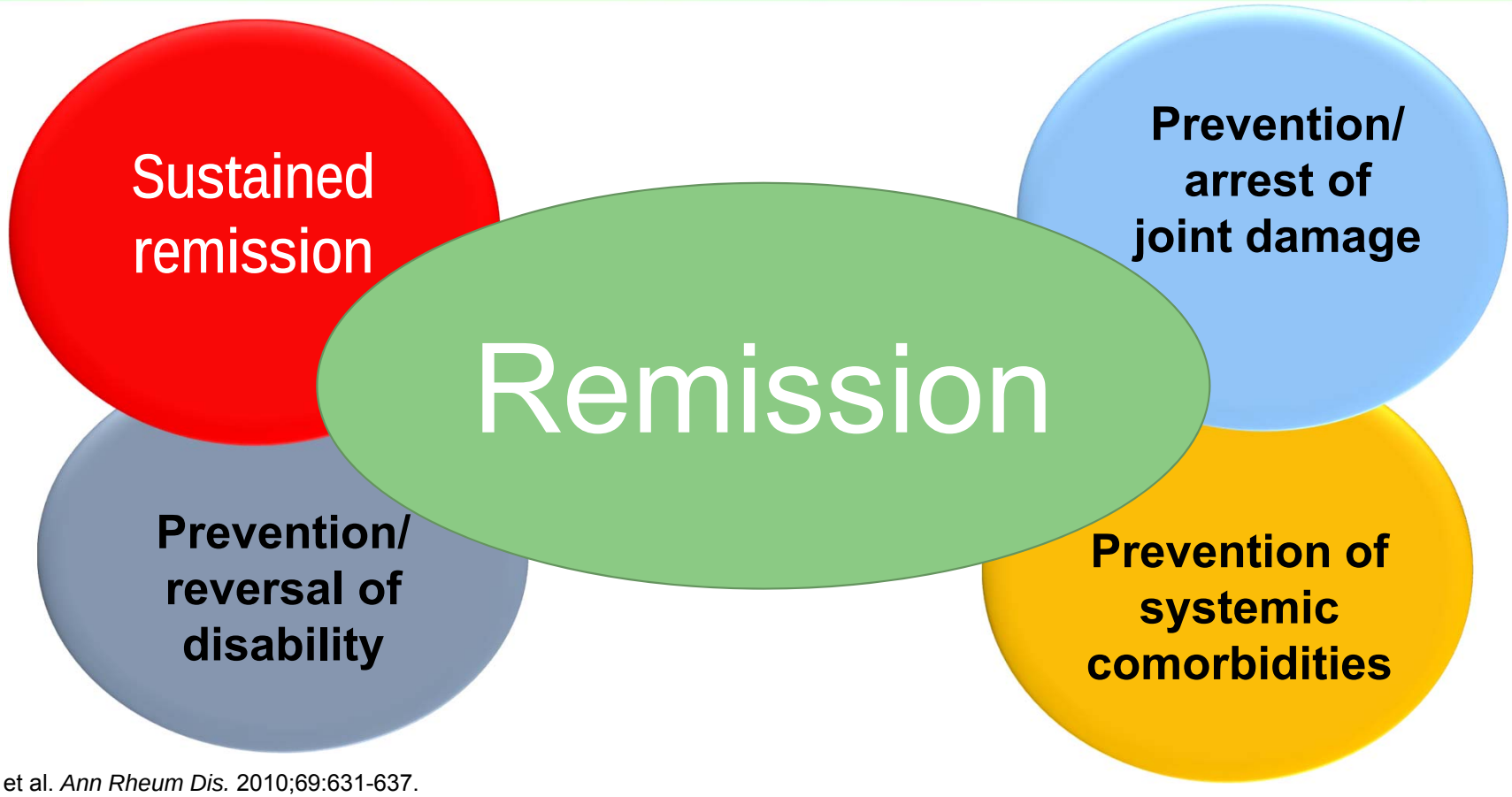
Progression of RA



- Inflammatory joint symptoms determine disability early in natural history of the disease
- Joint destruction dominates disability late in disease

Adapted from Kirwan JR. *J Rheumatol.* 2001;28:881-886.

RA Therapeutic Objectives



Smolen JS, et al. *Ann Rheum Dis.* 2010;69:631-637.

RA Treatment Strategy

Early and Intensive Treatment
Attenuate inflammation quickly

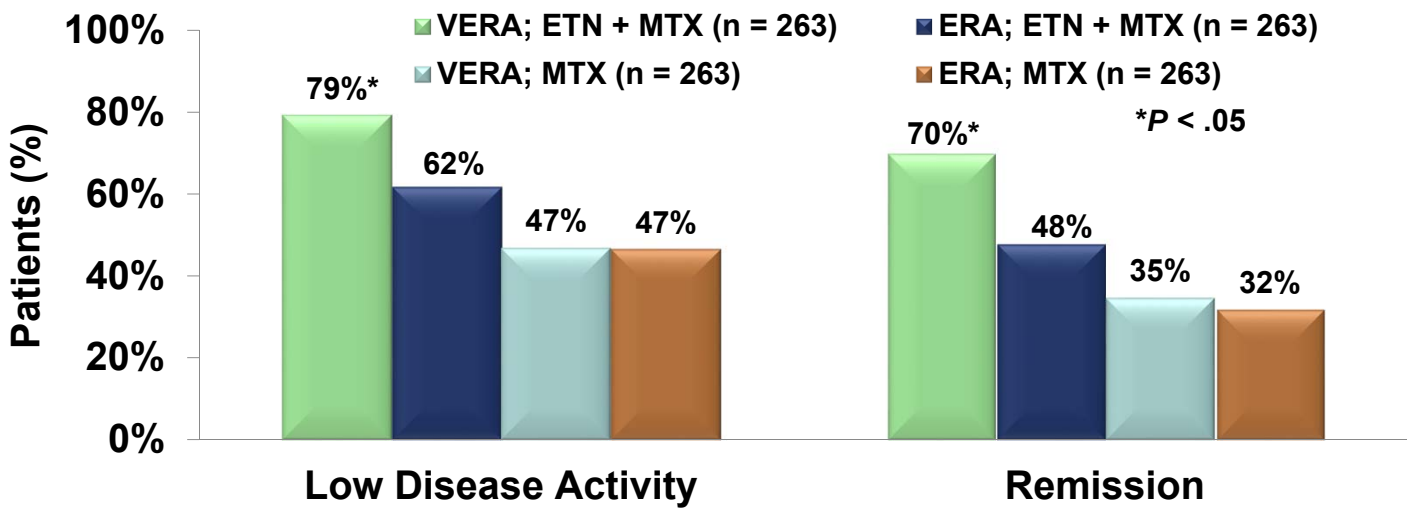
Treat-to-Target
Achieve remission with minimal/no signs or symptoms of active inflammation

Achieve Tight Control
Maintain remission or a low level of disease activity over time

Smolen JS, et al. *Ann Rheum Dis.* 2015;0:1-13.
Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Early and Aggressive Treatment Elicits Greater Disease Control

Disease Activity and DAS28 Remission at 52 Weeks (Data from the COMET Trial)



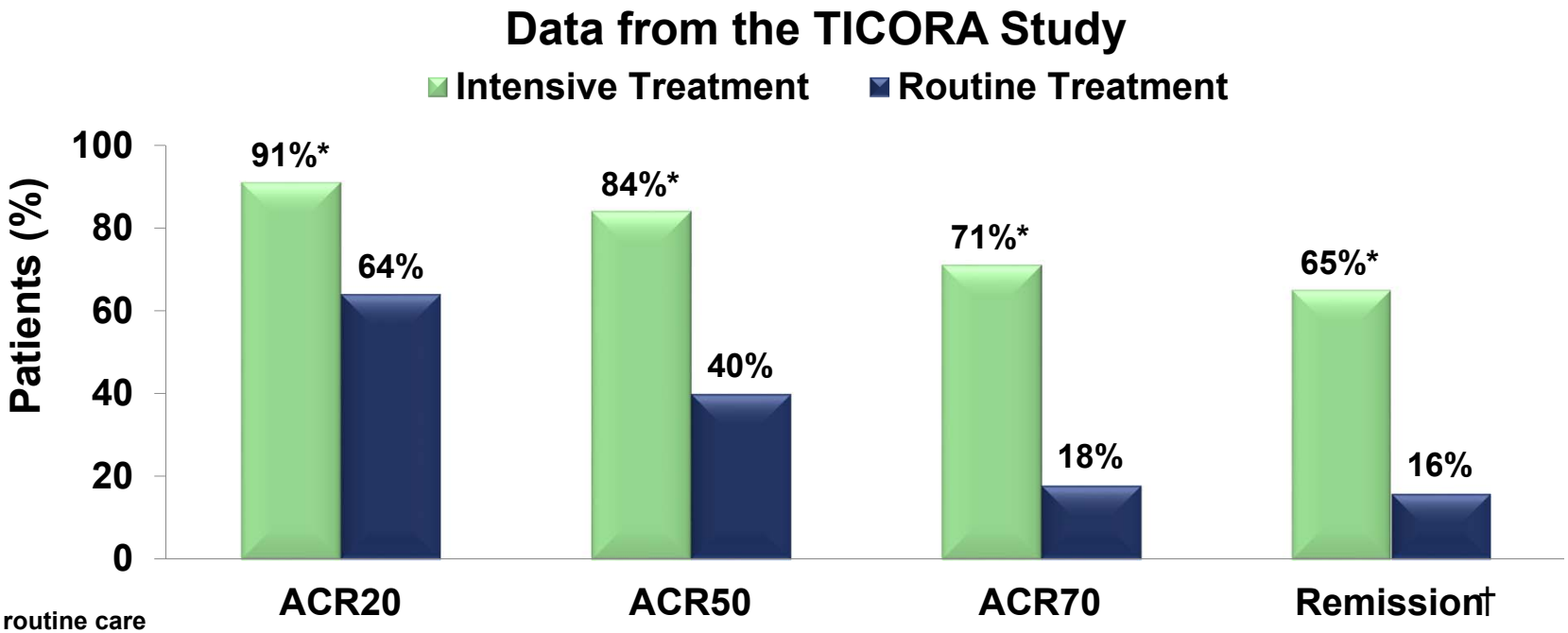
Randomized, double-blind, parallel treatment trial of MTX-naïve patients with moderate to severe early RA (n = 542)

A higher proportion of patients with *very early* RA achieved low disease activity and remission when treated more aggressively

COMET=combination of methotrexate and etanercept in active early RA; DAS28=28-joint Disease Activity Score; DMARD=disease-modifying antirheumatic drug; ERA=early rheumatoid arthritis; ETN=etanercept; MTX=methotrexate; TNF=tumor necrosis factor; VERA=very early rheumatoid arthritis.

Emery P, et al. *Ann Rheum Dis.* 2012;71:989-992.

Treat-to-Target Elicited Remission in 65% of RA Patients



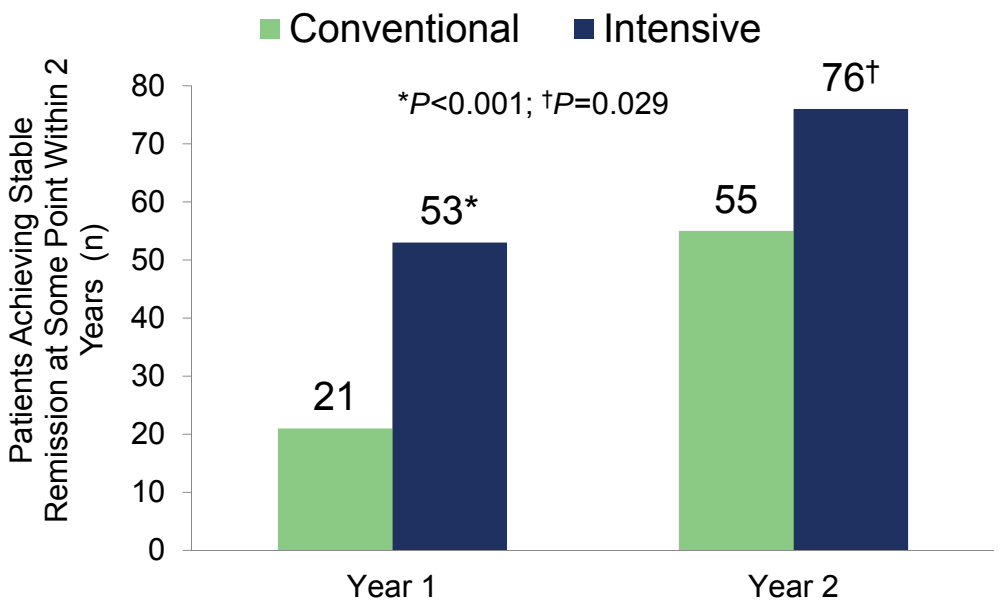
***P* < .0001 vs routine care**
†Disease activity score < 1.6
Intention-to-treat population; n = 111 patients with RA duration < 5 years.

ACR20=American College of Rheumatology 20% improvement criteria; ACR50=American College of Rheumatology 50% improvement criteria; ACR70=American College of Rheumatology 70% improvement criteria; TICORA=Tight Control for Rheumatoid Arthritis

Grigor C, et al. *Lancet*. 2004;364:263-269.

Treatment Intensification Achieves Remission More Often, Faster, and For a Longer Period of Time

Data from the CAMERA Study‡

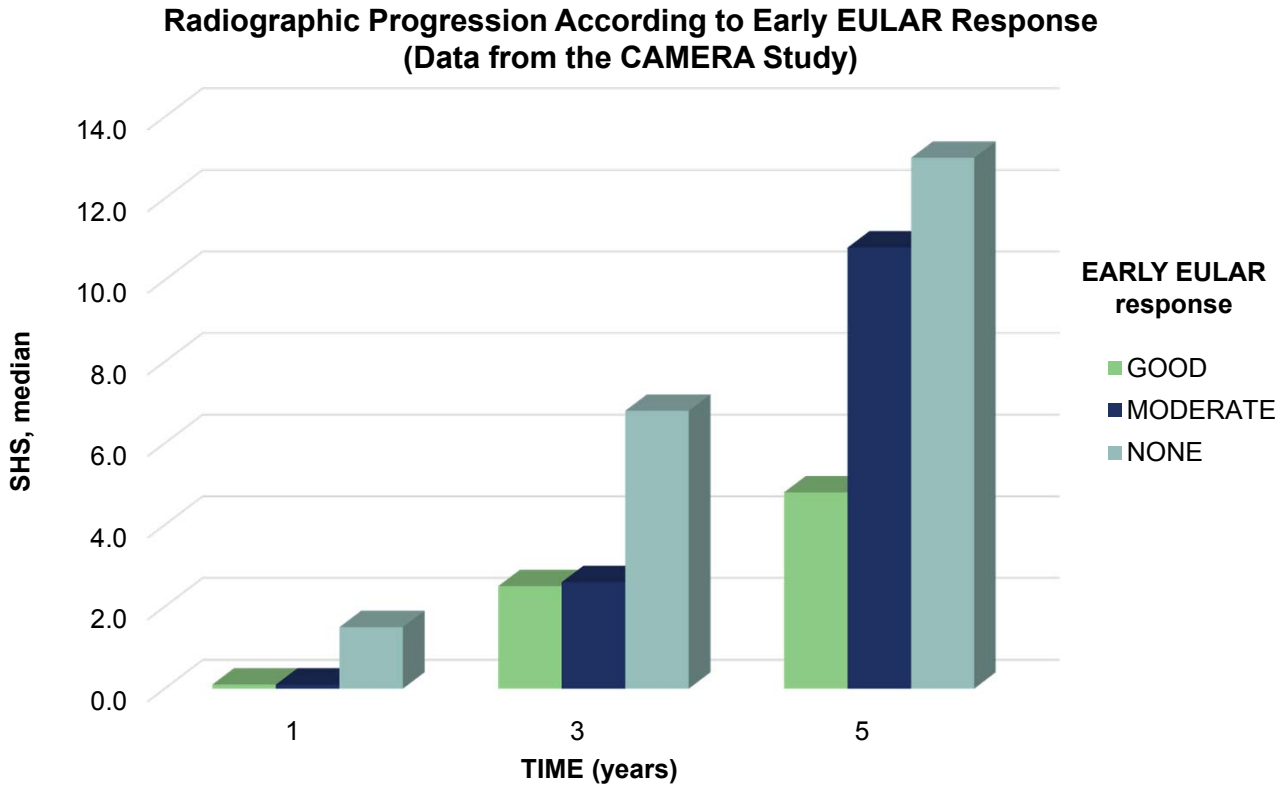


	Conventional	Intensive	*P* value
Time to remission, mo. (95% CI)	14.3 (12.6 – 16.1)	10.4 (9.1 – 11.7)	<0.001
Duration of remission, mo. (95% CI)	9.1 (7.6 – 10.6)	11.6 (10.1 – 13.1)	0.025
Median Area Under the Curve ($IQ_{0.25-0.75}$)			
Morning stiffness	23.7 (12.3 – 56.7)	17.0 (7.5 – 41.2)	0.009
ESR	21.6 (13.0 – 33.6)	17.7 (10.2 – 27.6)	0.007
Tender joint count	5.5 (2.8 – 9.2)	3.6 (1.9 – 6.0)	<0.001
Swollen joint count	4.7 (2.8 – 7.6)	2.7 (1.5 – 5.2)	<0.001

‡Two-year, multicenter, open-label trial of intensive treatment with methotrexate (MTX0 vs conventional therapy. Patients in both groups received MTX (n=299). Patients in the intensive treatment group came to the outpatient clinic once every month; adjustment of the MTX dosage was tailored to the individual patient on the basis of predefined response criteria. Patients of the conventional strategy group came to the outpatient clinic once every three months; they were treated according to common practice.

Verstappen SM, et al. *Ann Rheum Dis*. 2007;66:1443–1449.

Early Treatment with Intensive DMARD Therapy Slows Radiographic Progression



EULAR=European League Against Rheumatism; SHS=Sharp van der Heijde score (median values)

Rantalaiho V, et al. *Arthritis Res Ther*. 2010;12:R122.; Monti s, et al. *RMD Open*. 2015;1(Supp; 1):e000057. doi:10.1136/rmdopen-2015-000057.

Barriers to RA Disease Control

- Factors associated with no adjustment in RA therapy despite documented high or moderate disease activity

Barriers
Irreversible joint damage
Patient-driven preference for current therapy
Non-inflammatory muscle pain
Insufficient time to assess effect of recently initiated RA therapy
Safety concerns
Presence of comorbid conditions
Resistant disease

Tymms K, et al. *Arthritis Care Res* . 2014;66:190-196.

Feasibility of Treat-to-Target Strategy in Clinical Practice

- Success is highly dependent on physician adherence to the strategy in the clinical setting[1]
- Maksymowych et al observed that in 30% to 60% of clinic visits, therapy intensification was not implemented after documentation of moderate to high RA disease activity by any metric[2]
- In nearly 70% of the cases, the primary reason for not following a treat-to-target approach was a belief that current treatment was “acceptable”[3]

1. Lesuis N, et al. RMD Open. 2016;2:e000195; 2. Maksymowych WP, et al. Arthritis Rheum. 2014;66:S1272; 3. Waimann CA, et al. Arthritis Rheum. 2014;66:S1037.

Measures of Disease Activity and Progression Guide Treatment Decisions

Use validated measurements of disease activity/progression to guide treatment decisions and achieve tight control of RA[1]

Biomarkers of inflammation[2]

- ESR and CRP are acute-phase response measures scored as normal or abnormal based on local laboratory standards
  - If results of at least 1 of these 2 tests are abnormal, patient should be scored as having an abnormal acute-phase response

Disease activity scales[1,3-5]

- American College of Rheumatology 20% improvement criteria (ACR20)
- Disease Activity Score-28 (DAS28)
- Simplified Disease Activity Score (SDAI)
- Clinical Disease Activity Score (CDAI)
- Easy Rheumatoid Arthritis Measure (ERAM)
- Global Arthritis Scale (GAS)
- Routine Assessment of Patient Index Data 3 (RAPID3)

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate.

1. Smolen JS, et al. *Ann Rheum Dis.* 2015;0:1-13. 2. Aletaha D, et al. *Arthritis Rheum.* 2010;62:2569-2581. 3. Hobbs KF, et al. *Rheumatology (Oxford).* 2012;51 Suppl 6:vi21-27. 4. Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26. 5. Anderson J, et al. *Arthritis Care Res (Hoboken).* 2012;64:640-647.

Disease Activity Measures Provide Insight on Patient Response to Treatment

Instrument	Thresholds of Disease Activity
Patient Activity Scale (PAS) or PASII (range 0–10)	Remission: 0–0.25 Low activity: >0.25–3.7 Moderate activity: >3.7 to <8.0 High activity: ≥8.0
Routine Assessment of Patient Index Data 3 (RAPID3) (range 0–10)	Remission: 0–1.0 Low activity: >1.0–2.0 Moderate activity: >2.0–4.0 High activity: >4.0–10
Clinical Disease Activity Index (CDAI) (range 0–76.0)	Remission: ≤2.8 Low activity: >2.8–10.0 Moderate activity: >10.0–22.0 High activity: >22
Disease Activity Score (DAS) 28 erythrocyte sedimentation rate (ESR) (range 0–9.4)	Remission: <2.6 Low activity: ≥2.6 to,3.2 Moderate activity: ≥3.2 to #5.1 High activity: >5.1
Simplified Disease Activity Index (SDAI) (range 0–86.0)	Remission: ≤3.3 Low activity: >3.3 to ≤11.0 Moderate activity: >11.0 to ≤26 High activity: >26

Singh JA, et al. *Arthritis Rheumatol.* 2016;68:1-26.

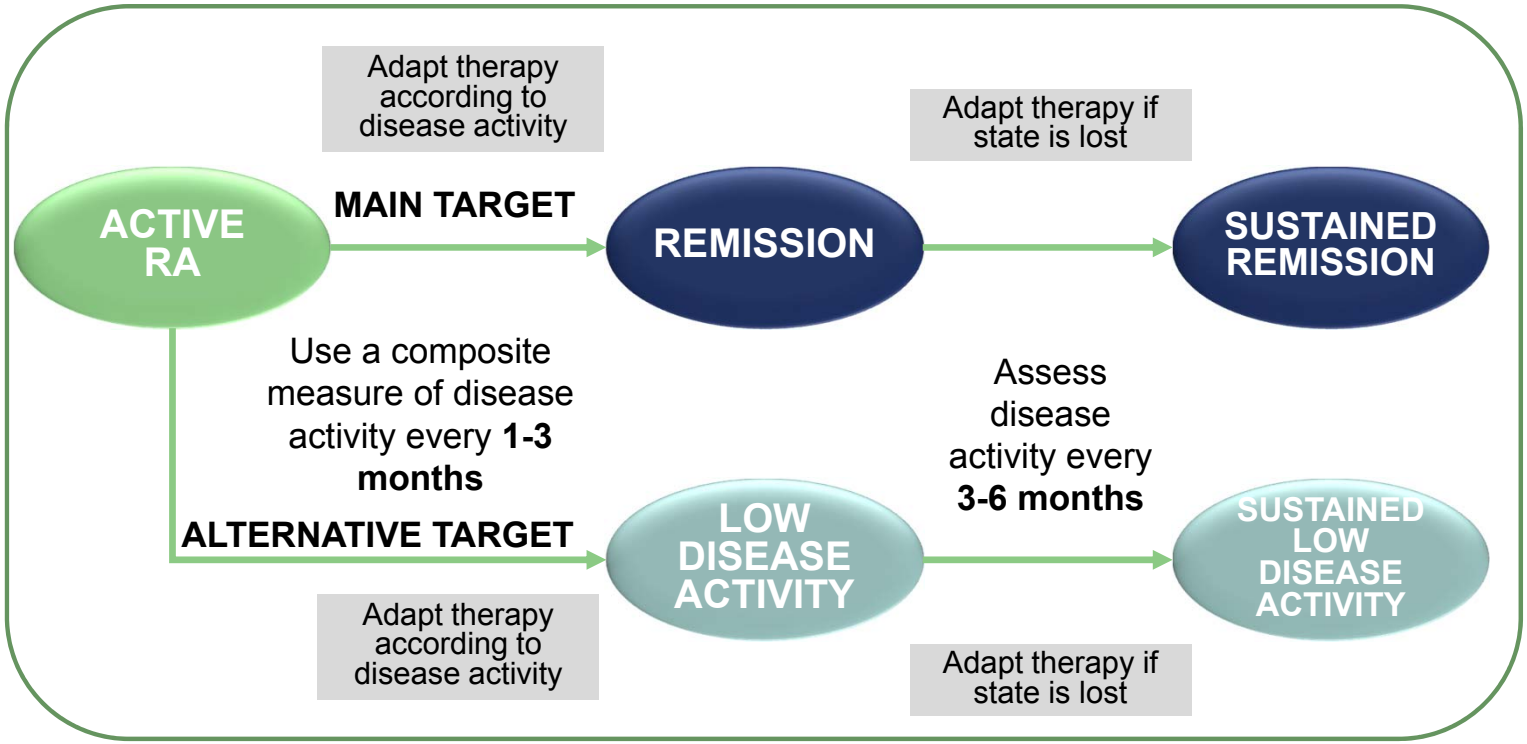
Routine Objective Measurement of Disease Activity Associated with Remission

Trial	Factors Associated With Remission	Outcome
TICORA[1]	• Intense treatment • Frequent assessments • Predetermined thresholds for escalation of therapies	10x higher rate of remission in patients receiving frequent objective assessment and intense therapy vs routine care
BeST[2]	• Frequent assessments • Early escalation to combination therapy	Greater number of patients receiving frequent objective assessment and early escalation of therapy achieved remission vs routine care

BeST=The Dutch Behandel Strategieen study; TICORA=tight control for rheumatoid arthritis study.

1. Grigor C, et al. *Lancet*. 2004;364:263-269. 2. Goekoop-Ruiterman YP, et al. *Ann Intern Med*. 2007;146:406-415.

Treat-to-Target Algorithm



Smolen JS, et al. *Ann Rheum Dis.* 2015;0:1-13.

Pharmacologic Management of RA: Guiding Principles

Duration of therapeutic response varies

Long-term RA treatment often involves a sequence of different therapies

Optimal sequencing determined by disease activity, response to therapy, and drug mechanism of action

Rendas-Baum R, et al. *Arthritis Res Ther.* 2011;13:R25.

Pharmacologic Interventions

Corticosteroids

- Methylprednisolone
- Prednisone
- Prednisolone

Conventional DMARDs

- Azathioprine
- Hydroxycholorquine
- Leflunomide
- Methotrexate
- Sulfasalazine

Biologic DMARDs

- TNF inhibitors
- IL-1 inhibitors
- B-cell agents
- T-cell agents
- IL-6 inhibitors
- JAK inhibitors

DMARD=disease modifying anti-rheumatic drugs; JAK=Janus Kinase inhibitor; TNF=Tumor Necrosis Factor.

Corticosteroids

Drug	Initial US Approval	Brand Name	Route of Administration	Mechanism of Action
Prednisone	1955	Generic	Oral	Anti-inflammatory and immunomodulator
Prednisolone[1]	1955	Orapred ODT®	Oral	
Methylprednisolone[2-4]	1957	Medrol®	Oral	
		Solu-Medrol®	IV infusion or IM injection (in office)	
		Depo-Medrol®	IA, IL, IM, or soft tissue injection (in office)	

IA=intraarticular; IL=intralesional; IM=intramuscular; IV=intravenous, ODT=orally disintegrating tablet.

1. Orapred ODT® [PI]. Florham Park, NJ: Shionogi Inc.; 2013. 2. Medrol® [PI]. New York, NY: Pharmacia & Upjohn Co.; 2013. 3. Solu-Medrol® [PI]. New York, NY: Pharmacia & Upjohn Co.; 2014. 4. Depo-Medrol® [PI]. New York, NY: Pharmacia & Upjohn Co.; 2014.

Nonbiologic Disease Modifying Antirheumatic Drugs

Drug	Initial US Approval	Brand Name	Route of Administration	Mechanism of Action
Sulfasalazine[1]	1950	Azulfidine®	Oral	Not well defined
Methotrexate[2,3]	1953	Generic	Oral	Dihydrofolate acid reductase inhibitor
		Otrexup™	SC injection	
Hydroxychloroquine[4]	1955	Plaquenil®	Oral	Not well defined
Azathioprine[5,6]	1968	Imuran®	Oral or IV infusion	Immunosuppressant
Leflunomide[7]	1998	Arava®	Oral	Pyrimidine synthesis inhibitor

1. Azulfidine® [PI]. New York, NY: Pfizer, Inc.; 2014. 2. Methotrexate [PI]. Morgantown, WV: Mylan Pharmaceuticals Inc.; 2013. 3. Otrexup™ [PI]. Ewing, NJ: Antares Pharma, Inc.; 2014. 4. Plaquenil® [PI]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2012. 5. Imuran ® for IV injection [PI]. San Diego, CA: Prometheus Laboratories Inc.; 2014. 6. Imuran ® [PI]. San Diego, CA: Prometheus Laboratories Inc.; 2014. 7. Arava ® [PI]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2014.

Currently Available Biologic Agents Indicated for the Treatment of RA

Drug	Initial US Approval	Brand Name	Route of Administration	Mechanism of Action
Etanercept[1]	1998	Enbrel®	SC injection	TNF inhibitor
Infliximab[2]	1998	Remicade®	IV infusion	TNF inhibitor
Anakinra[3]	2001	Kineret®	SC injection	IL-1 receptor inhibitor
Adalimumab[4]	2002	Humira®	SC injection	TNF inhibitor
Certolizumab pegol[5]	2008	Cimzia®	SC injection	TNF inhibitor
Golimumab[6]	2009	Simponi®	SC injection	TNF inhibitor
Rituximab[7]	1997	Rituxan®	IV infusion	B-cell agent (anti-CD20 antibody)
Abatacept[8]	2005	Orencia®	IV infusion or SC injection	T-cell agent (selective costimulator inhibitor)
Tocilizumab[9]	2010	Actemra®	IV infusion or SC injection	IL-6 inhibitor
Tofacitinib[10]	2012	Xeljanz®	Oral	JAK inhibitor

IL=interleukin; IV=intravenous; JAK=Janus kinase; SC=subcutaneous; TNF=tumor necrosis factor.

1. Enbrel® [PI]. Thousand Oaks, CA: Amgen Inc.; 2015. 2. Remicade® [PI]. Horsham, PA: Janssen Biotech, Inc.; 2015. 3. Kineret® [PI]. Stockholm, Sweden: Swedish Orphan Biovitrium AB; 2012. 4. Humira® [PI]. North Chicago, IL: AbbVie Inc.; 2014. 5. Cimzia® [PI]. Smyrna, GA: UCB, Inc.; 2013. 6. Simponi® [PI]. Horsham, PA: Janssen Biotech, Inc.; 2014. 7. Rituxan® [PI]. S. San Francisco, CA: Genentech, Inc.; 2014. 8. Orencia® [PI]. Princeton, NJ: Bristol-Myers Squibb Company; 2015. 9. Actemra® [PI]. South San Francisco, CA: Genentech, Inc.; 2014. 10. Xeljanz® [PI]. New York, NY: Pfizer, Inc.; 2015.

Emerging RA Therapies

Drug	Mechanism of Action	Status
Baricitinib	JAK1/2 inhibitor	Phase 3
Filgotinib	JAK1 inhibitor	Phase 2
ABT-494	JAK1 inhibitor	Phase 3
Sarilumab	IL-6R antagonist	Phase 3
Sirukumab	IL-6 inhibitor	Phase 3
Vobarilizumab (ALX 0061)	IL-6R antagonist	Phase 2
Clazakizumab	IL-6 inhibitor	Phase 2
Denosumab	RANKL inhibitor	Phase 3
Mavrilimumab	GM-CSF antagonist	Phase 2

JAK=Janus kinase; IL=interleukin; RANKL, receptor activator of NF-κB ligand ; GM-GSF=granulocyte–macrophage colony-stimulating factor.

Chaudhari K, et al. *Nat Rev Drug Discov*. 2016;15:305-306.

Summary

Treatment Goals	• Achieve remission, relieve symptoms, prevent joint and organ damage, improve physical function and well-being, and reduce long-term complications
Treatment Strategy	• Early and aggressive treatment • Treat-to-target (remission) • Achieve tight control through individualized therapy
Measures of Disease Activity/Progression	• Use validated measurements to guide treatment decision-making
Pharmacologic Management	• Long-term treatment often involves a sequence of different therapies • Optimal sequencing is determined by response, disease progression, and effects of therapies on disease pathways

Current Practice Guidelines Review

Edmund Pezalla, MD, MPH

CEO

Enlightenment Bioconsulting

Hartford, CT

Learning Objective

- Discuss current evidence-based rheumatoid arthritis (RA) treatment guidelines

Evolution of the American College of Rheumatology (ACR) RA Treatment Recommendations

2008

Recommendations for the use of nonbiologic and biologic DMARDs when starting or resuming therapy[1]

2012

Update of the 2008 recommendations, including switching drugs[2]

2015

Update of the 2012 recommendations including treat-to-target, tapering, discontinuation of therapy, use of biologics in patients with comorbidities[3]

DMARDs=disease-modifying antirheumatic drugs.

1. Saag KG, et al. *Arthritis Rheum.* 2008;59:762-784; 2. Singh JA, et al. *Arthritis Care Res (Hoboken).* 2012;64:625-639; 3. Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Principles Guiding the Treatment of RA

- **Focus on common or everyday patients**
- **Cost is a consideration in these recommendations**
- **Measure disease activity using an ACR-recommended measure in a majority of encounters for RA patients**
- **Routinely perform functional status assessment using a standardized, validated measure at least once per year and more frequently if disease in active disease**
- **If a patient has low RA disease activity or is in clinical remission, switching from one therapy to another should be considered only at the discretion of the treating physician in consultation with the patient**
- **A recommendation favoring one medication vs another means the preferred medication is the recommended first option. However, a nonfavored medication may still be a potential option under certain conditions.**

ACR=American College of Rheumatology; MTX=methotrexate.

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Current ACR Guidelines Provide Recommendations on Six Primary Topics

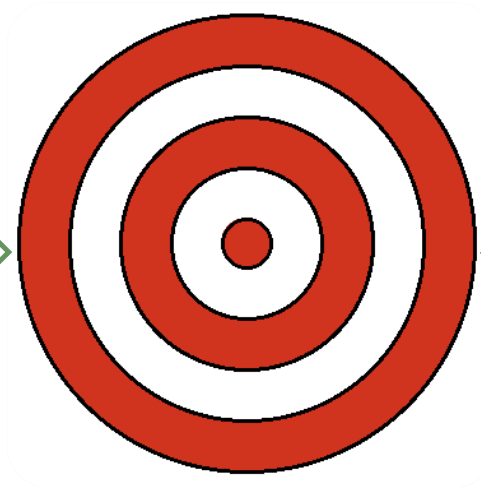
1	• Treat-to-target approach, tapering, and discontinuing medications
2	• Assess disease activity using validated tools/instruments
3	• Employ intensive therapy in early (<6 mo) and established RA (>6 mo)
4	• Use of biologics in high-risk RA patients with comorbidities
5	• Vaccination of RA patients starting/receiving DMARDs or biologics
6	• Screening for TB in patients starting/receiving biologics or tofacitinib

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Treat-to-Target

Targets

- **Low disease activity**
- **Remission**
- **Other appropriate targets selected by the clinician and patient**



Functional Assessment

- **Assessment using validated tools**
- **Conduct at least once per year and more often in active RA**

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

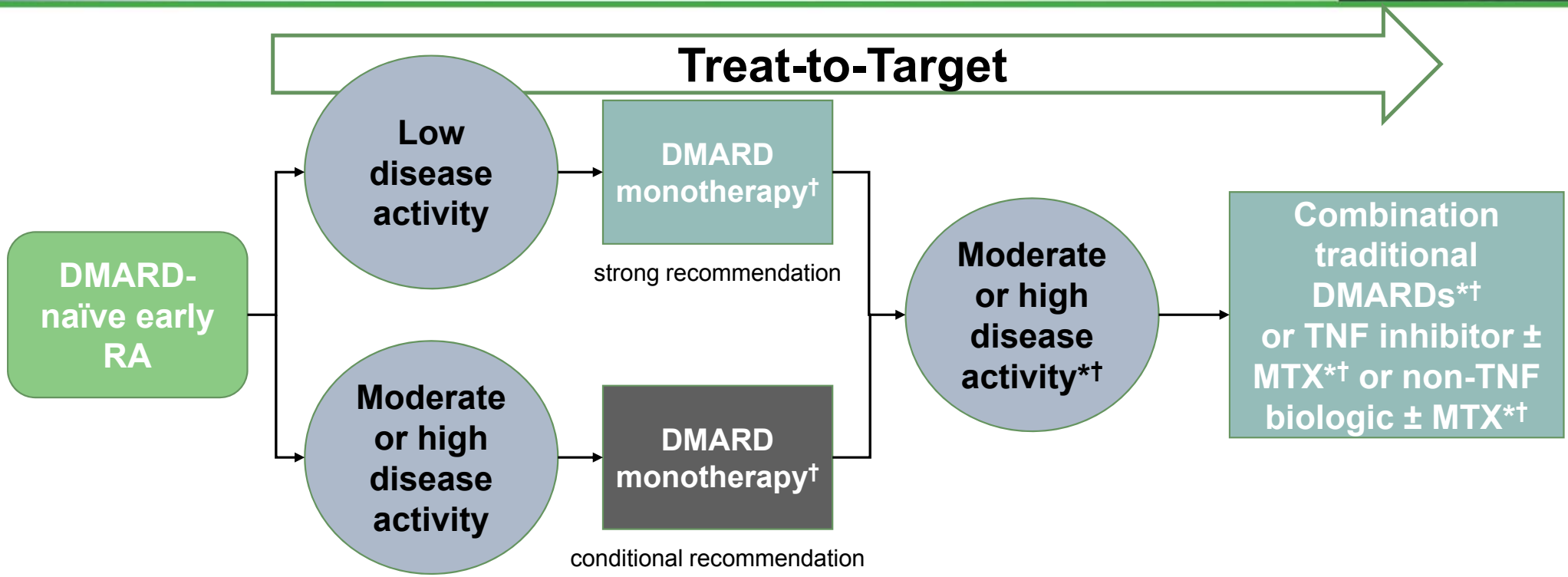
Instruments to Assess RA Disease Activity

- Clinical Disease Activity Index (CDAI)
  - Range: 0 - 76
- Disease Activity Score based on 28 joint count (DAS28) or erythrocyte sedimentation rate (ESR)
  - Range: 0 – 9.4
- Patient Activity Scale (PAS) or PAS II
  - Range: 0 – 10
- Routine Assessment of Patient Index Data 3 (RAPID3)
  - Range: 0 - 10
- Simple Disease Activity Index (SDAI)
  - Range: 0 - 86

The specific tool used does not matter; it's more important to routinely assess disease activity

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.
Anderson J, et al. *Arthritis Care Res (Hoboken).* 2012;64:640-647.

Recommended Treatment Algorithm for Early RA



*Consider adding low-dose glucocorticoids in patients with moderate or high RA disease activity when starting DMARDs and in patients with DMARD or biologic failure; †Also consider short-term glucocorticoids (<3 months) for RA disease flares. Non-TNF biologics include abatacept, rituximab, or tocilizumab

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Recommendations for the Treatment of Patients with Established RA (1 of 3)

Recommendations for Patients with Established RA	Level of Evidence
1. Regardless of disease activity level, use a treat-to-target strategy	**Moderate**
2. If disease activity is low, in patients who have never taken a DMARD, use DMARD monotherapy (MTX preferred) over a TNFi	**Low**
3. If disease is moderate or high in patients who have never taken a DMARD • Use DMARD monotherapy (MTX preferred) over tofacitinib • Use DMARD monotherapy (MTX preferred) over combination DMARD therapy	 High Moderate
4. If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs *or* add a TNFi *or* a non-TNF biologic *or* tofacitinib (all choices with or without MTX) rather than continuing DMARD monotherapy alone	**Moderate to Very Low**
5. If disease activity remains moderate or high despite TNFi therapy in patients who are currently not on DMARDs, add one or two DMARDs to TNFi therapy rather than continuing TNFi therapy alone	**High**

Blue and bolded = strong recommendation

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Recommendations for the Treatment of Patients with Established RA (2 of 3)

Recommendations for Patients with Established RA	Level of Evidence
6. If disease activity remains moderate or high despite use of a single TNFi: • Use a non-TNF biologic, with or without MTX, over another TNFi with or without MTX • Use a non-TNF biologic, with or without MTX, over tofacitinib with or without MTX	Low to Very Low Very Low
7. If disease activity remains moderate or high despite use of a single non-TNF biologic, use another non-TNF biologic, with or without MTX, over tofacitinib, with or without MTX	Very Low
8. If disease activity remains moderate or high despite use of multiple (2+) sequential TNFi therapies, first use a non-TNF biologic, with or without MTX, over another TNFi or tofacitinib (with or without MTX)	Very Low
9. If disease activity still remains moderate or high despite the use of multiple TNFi therapies, use tofacitinib, with or without MTX, over another TNFi, with or without MTX, if use of a non-TNF biologic is not an option	Low
10. If disease is moderate or high despite use of at least one TNFi and at least one non-TNF biologic: • First use another TNF biologic, with or without MTX, over tofacitinib • If disease activity remains moderate or high, use tofacitinib, with or without MTX, over another TNFi	Very Low Very Low

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

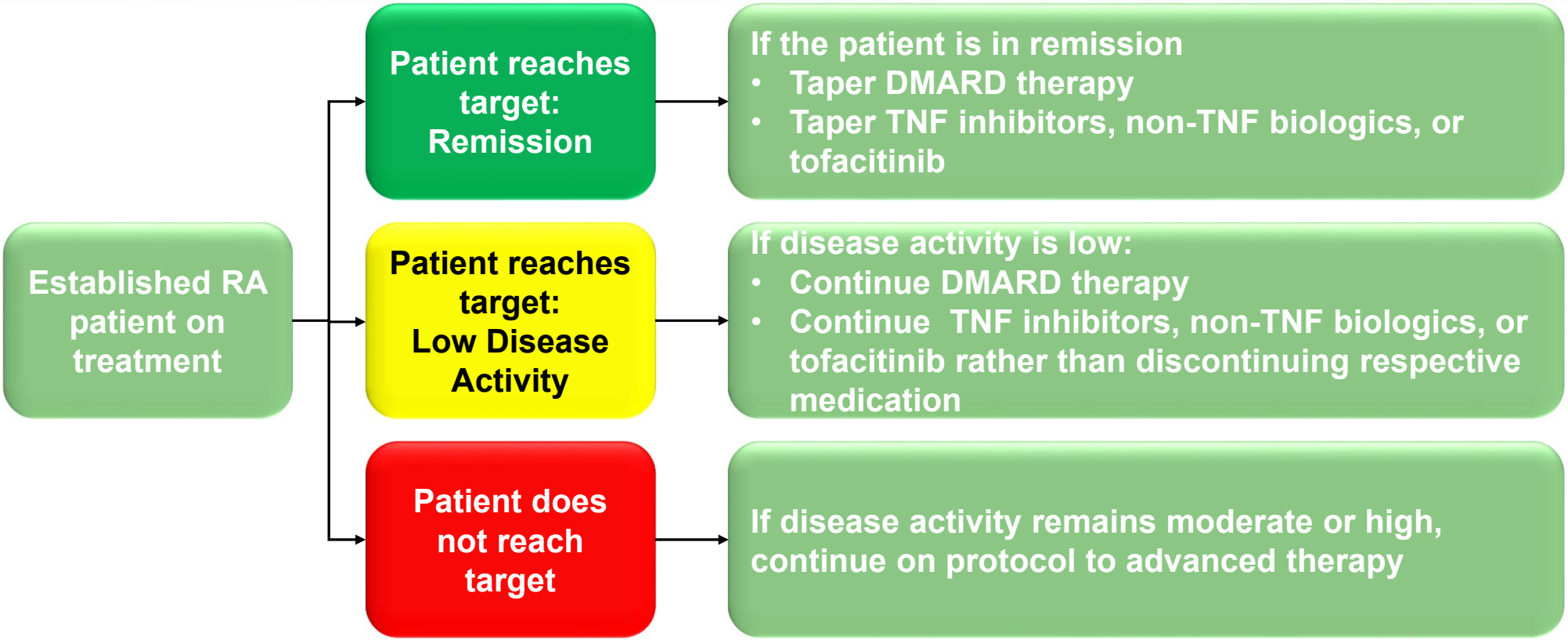
Recommendations for the Treatment of Patients with Established RA (3 of 3)

Recommendations for Patients with Established RA	Level of Evidence
11. If disease activity remains moderate or high despite use of DMARDs, TNFi, or non-TNF biologic therapy, add short-term, low-dose glucocorticoid therapy	High to Moderate
12. If disease flares in patients on DMARDs, TNFi, or non-TNF biologic therapy, add short-term glucocorticoids at the lowest possible dose and the shortest possible duration	Very Low
13. If the patient is in remission: • Taper DMARD therapy • Taper TNFi, non-TNF biologic, or tofacitinib (also see #15)	Low Moderate to Very Low
14. If disease activity is low: **• Continue DMARD therapy** **• Continue TNFi, non-TNF biologic, or tofacitinib rather than rather than discontinuing respective medication**	**Moderate** **High to Very Low**
15. If the patient's disease is in remission, DO NOT discontinue all RA therapies	**Very Low**

Blue and bolded = strong recommendation

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Recommended Treatment Algorithm for Established RA



Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Recommendations for the Treatment of RA Patients with High-Risk Comorbidities (1 of 2)

Comorbid Condition	Recommendation	Level of Evidence
Congestive Heart Failure (CHF)		
CHF	Use combination DMARDs *or* non-TNF biologics *or* tofacitinib *over* TNFi	Moderate to Very Low
CHF Worsening on Current TNFi Therapy	Use combination DMARDs *or* non-TNF biologics *or* tofacitinib *over* another TNFi	Very Low
Hepatitis B		
Active hepatitis B infection and receiving/received effective treatment	**Same recommendations as in patients without Hepatitis B**	**Very Low**
Hepatitis C		
Hepatitis C infection and receiving/received effective antiviral treatment	Same recommendations as in patients without Hepatitis B	Very Low
Hepatitis C infection and not receiving or requiring effective antiviral treatment	Use DMARDs *over* TNFi	Very Low

Blue and bolded = strong recommendation

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Recommendations for the Treatment of RA Patients with High-Risk Comorbidities (2 of 2)

Comorbid Condition	Recommendation	Level of Evidence
Past History of Treated or Untreated Malignancy		
Previously treated or untreated skin cancer (non-melanoma or melanoma)	Use DMARDs *over* biologics in melanoma Use DMARDs *over* tofacitinib in melanoma Use DMARDS *over* biologics in non-melanoma Use DMARDs *over* tofacitinib in non-melanoma	Very Low
Previously treated lymphoproliferative disorder	**Use rituximab *over* TNFi**	**Very Low**
Previously treated lymphoproliferative disorder	Use combination DMARD *or* abatacept or tocilizumab *over* TNFi	Very Low
Previously treated solid organ malignancy	Same recommendation as in patients without solid organ malignancy	Very Low
Previous Serious Infection		
Previous serious infection	Use combination DMARD *over* TNFi Use abatacept *over* TNFi	Very Low

Blue and bolded = strong recommendation

Singh J, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Caveats

- Current guidelines recommend employing multiple medications based on the patient's disease severity and progression instead of considering patient-specific factors that predict response to treatment
- Clinical guidelines consider the severity of the disease when deciding treatment, but do not include any prediction of drug efficacy

Singh JA, et al. *Arthritis Care Res*. 2012;64:625-639.
Spear BB, et al. *Trends Mol Med.* 2001;7:201-204.
Odgers DJ, et al. *AMIA Jt Summits Transl Sci Proc*. 2016;26:176-183.

Summary

- Current RA treatment guidelines emphasize
  - Treating-to-target in both early and established RA with the goal of achieving low disease activity or remission
  - Routinely assessing disease activity
  - Individualizing treatment
  - Treating patients with comorbid conditions
  - Tapering of therapy in patients in established remission

Analyzing the Available Data to Assess the Value of RA Treatment Options

Fadia Tohme-Shaya, PhD, MPH

Professor and Vice Chair for Academic Affairs

University of Maryland School of Pharmacy

Baltimore, MD

Learning Objectives

- Consider the economic outcomes and value of currently available therapy
- Evaluate the determinants of RA treatment value
- Understand the use of claim data in considering value

Burden of RA Extends Beyond the Joint

Ambulatory Care Events:

2.9 million ambulatory care visits each year

Comorbidity

5x higher CV disease event rate vs general population

QoL

Hospitalizations

>15,000 hospitalizations with RA listed as the principle diagnosis annually

Fatigue and Psychological Dysfunction

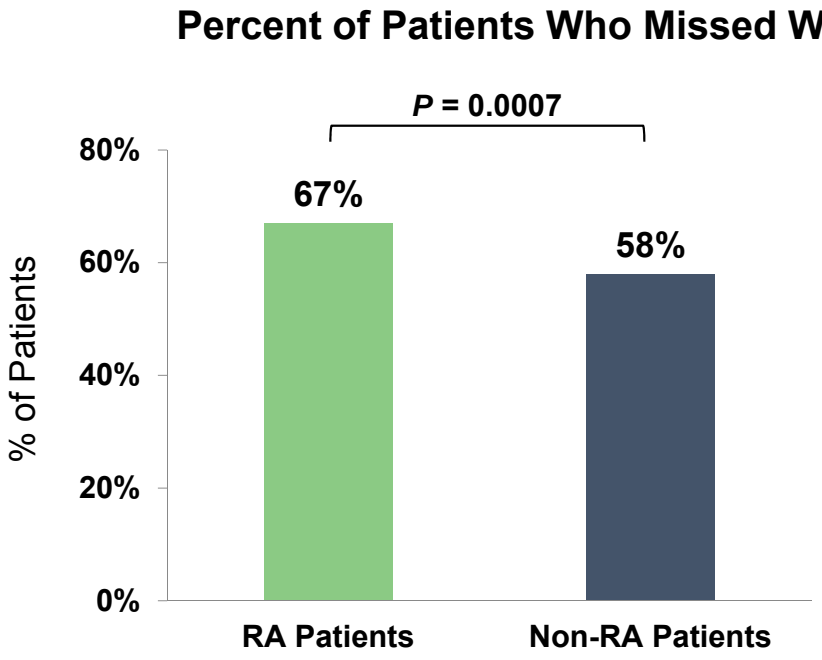
Up to 80% of patients report fatigue and an estimated 40% suffer depression

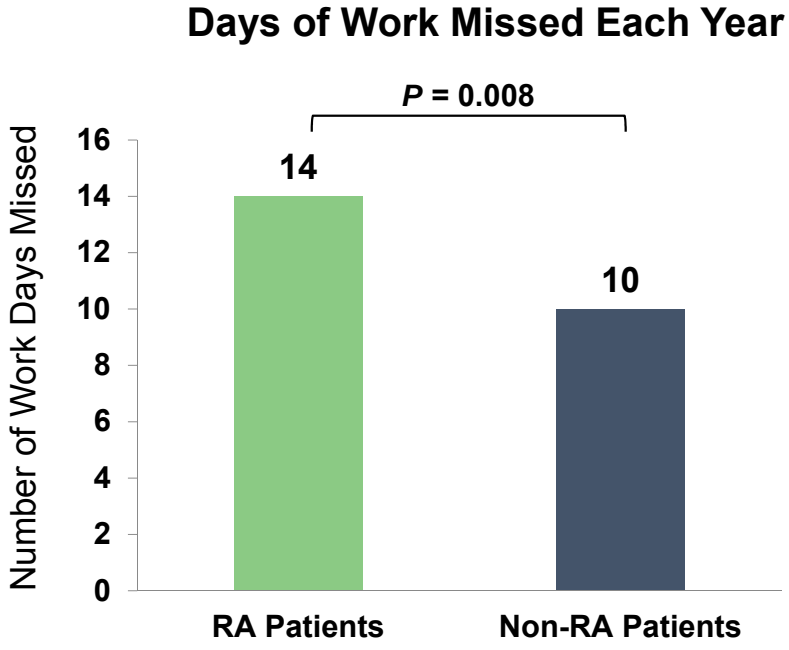
Reduced Life Expectancy

Mortality rate is 1.5 to 1.6-fold higher in RA patients vs general population

Centers for Disease Control. http://www.cdc.gov/arthritis/basics/rheumatoid.htm. Accessed February 2017.

RA Significantly Impairs Ability to Work

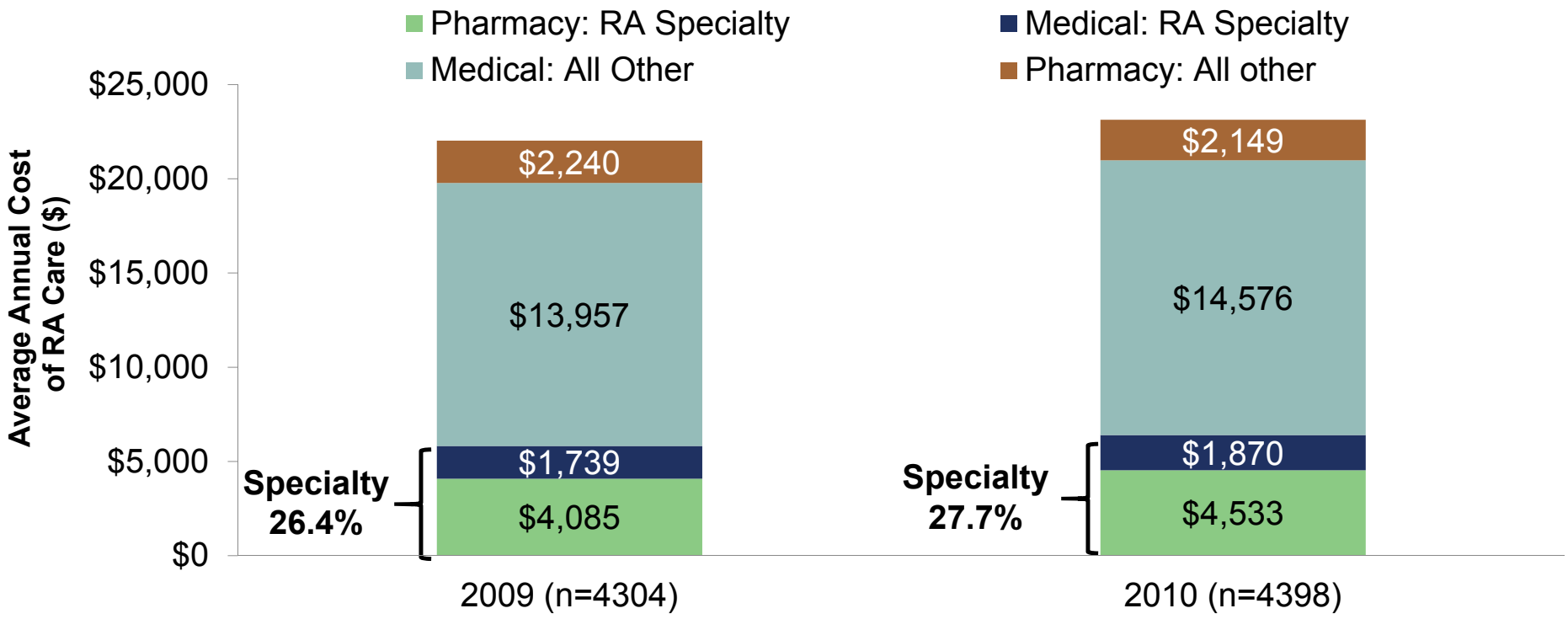




Retrospective analysis of employed individuals aged 18 to 65 using 1996–2006 US Medical Expenditure Panel Survey data.

Gunnarsson C, et al. *J Occupat Environ Med*. 2015;57:635-642.

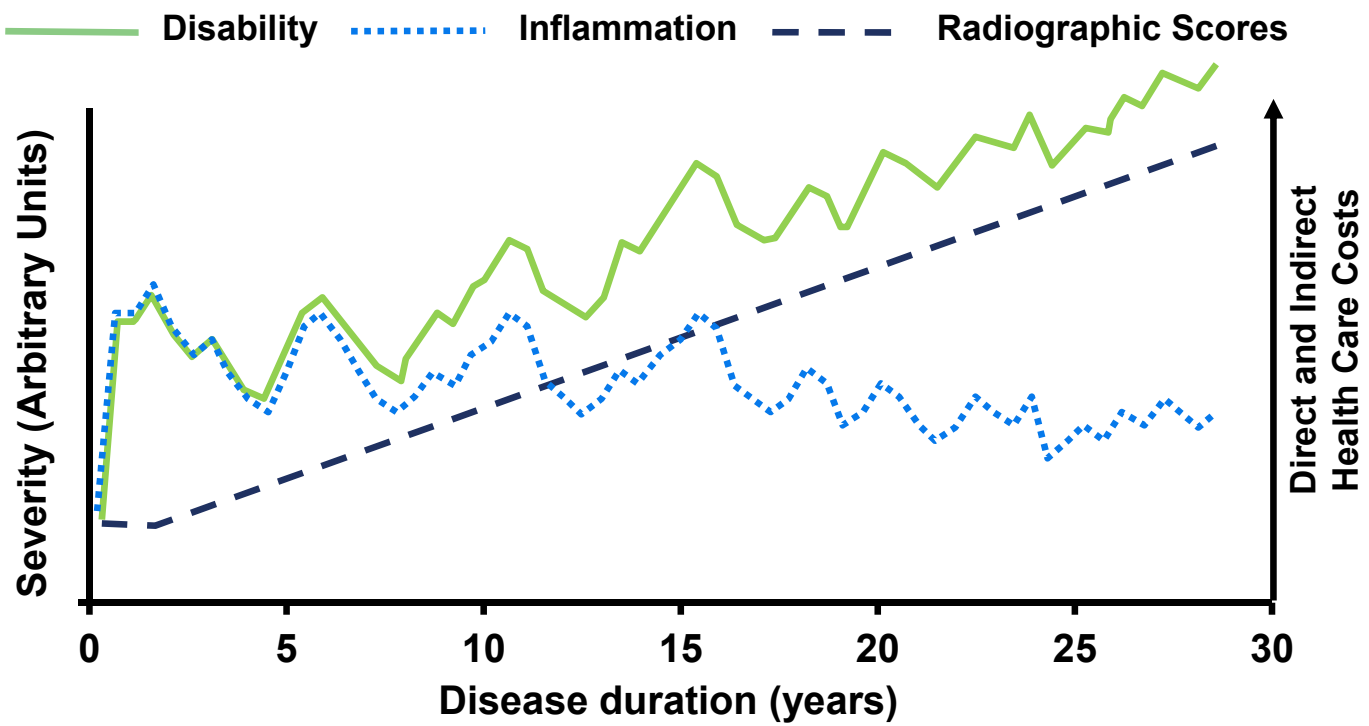
Economic Burden of RA on the Health Care System



Analysis of a commercially insured population made up of 1 million members, using integrated medical and pharmacy administrative claims data from 2008 to 2010.

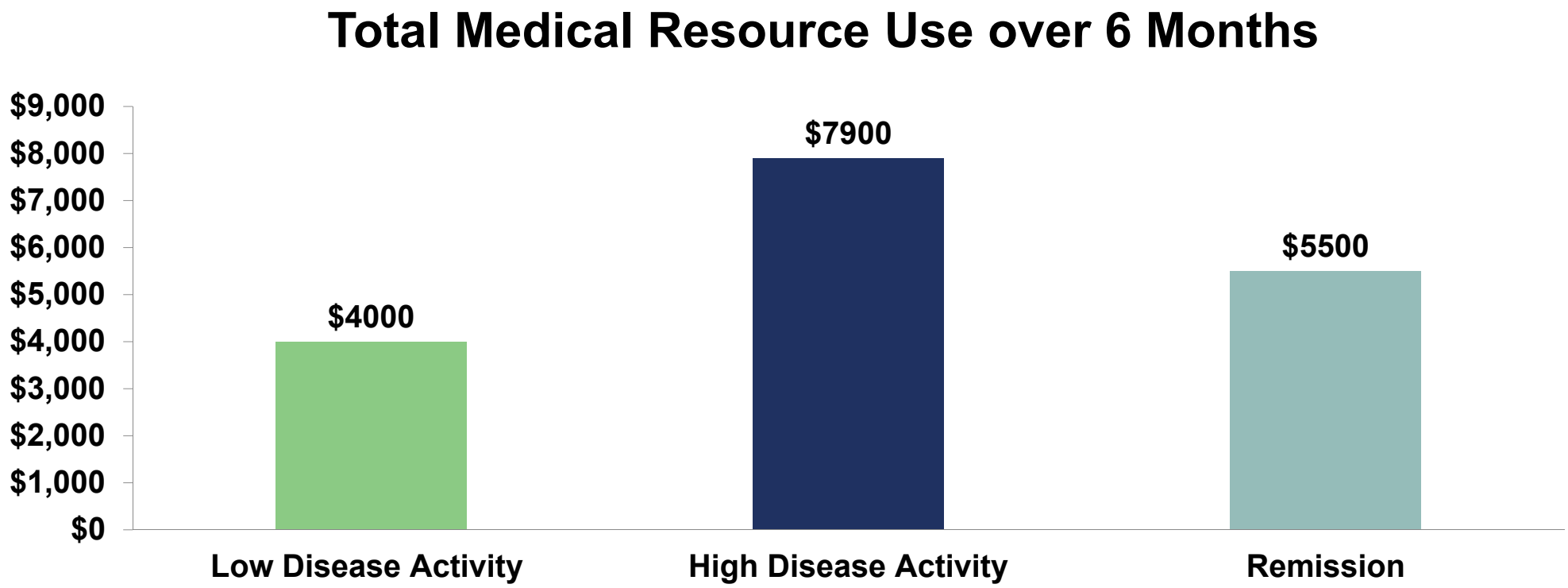
Gleason PP, et al. *J Manag Care Pharm.* 2013;19:542-48.

Cost of RA Treatment Increases Over Time as Function Declines



Kirwan J. *J Rheumatol*. 1999;26:720-725; Wolfe F, Cathey MA. *J Rheumatol*. 1991;18:1298-1306; Fautrel B. *Rheumatology*. 2012;51:Suppl 4:iv21-6.

Increased Medical Resource Utilization in Patients with High Disease Activity



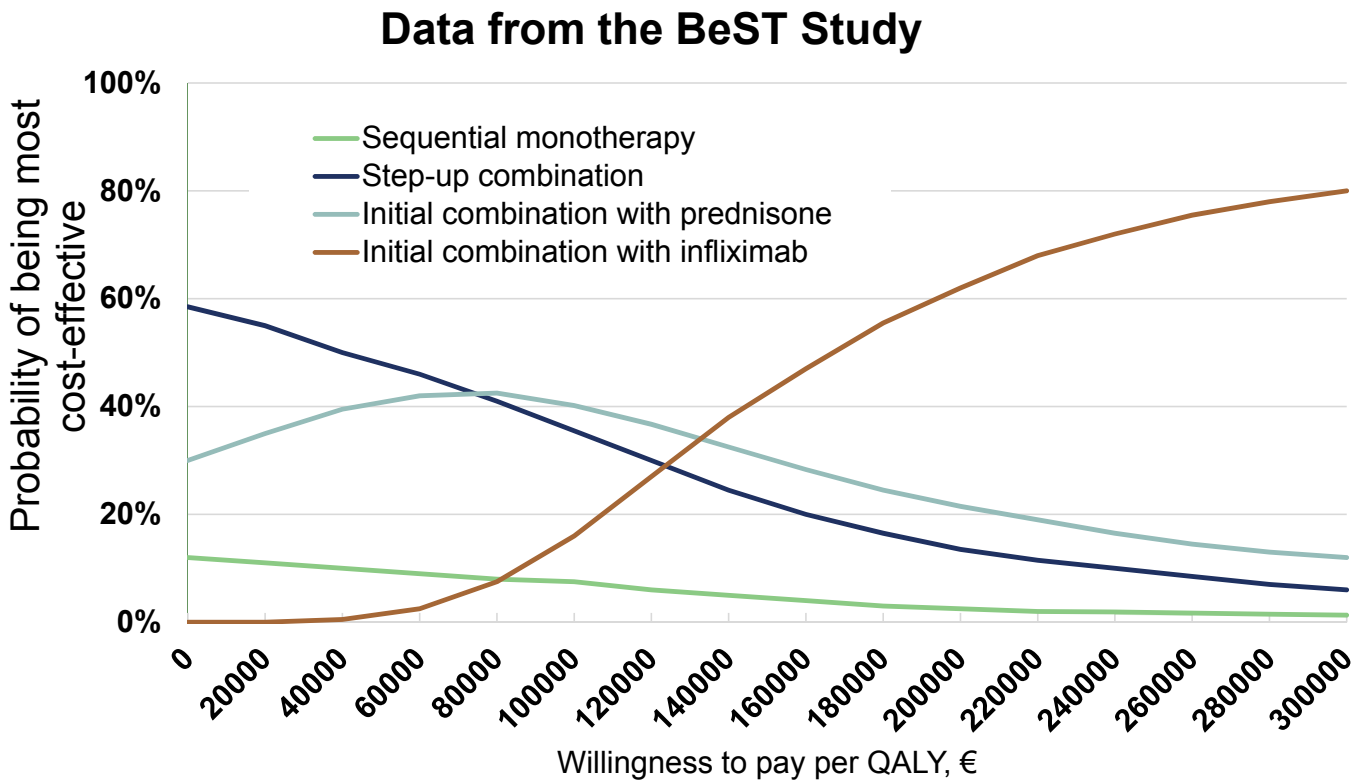
Beresniak A, et al. *Clin Exp Rheumatol*. 2013;31:400-408.

Determining the Value of RA Treatments

- Increases in the number and use of biologics make them an important target for economic evaluation
- Economic evaluation tools include
  - Cost-effectiveness analysis (CEA): Compares the cost and effectiveness of two or more treatments
  - Cost-utility analysis (CUA): Subtype of CEA that utilizes quality-adjusted life-years (QALY) as a measure of effectiveness
    - Primary outcome measure in CUA is the incremental cost-effectiveness ratio (ICER)
    - ICER describes the ratio of the additional costs of a treatment (vs an alternative) to QALYs gained

Joensuu JT, et al. *PLoS One.* 2015;10(3):e0119683.

Biologics Do Not Appear to be Cost-effective as First-line Therapy



- Anti-TNF agents are less cost-effective vs conventional DMARDs for newly diagnosed, treatment-naïve patients[1,2]

BeST=The Dutch Behandel Strategieen study.

1. Tsao NW, et al. *Best Pract Res Clin Rheumatol*. 2012;26:659-676; 2. van den Hout WB, et al. *Arthritis Rheum*. 2009;61:291-299.

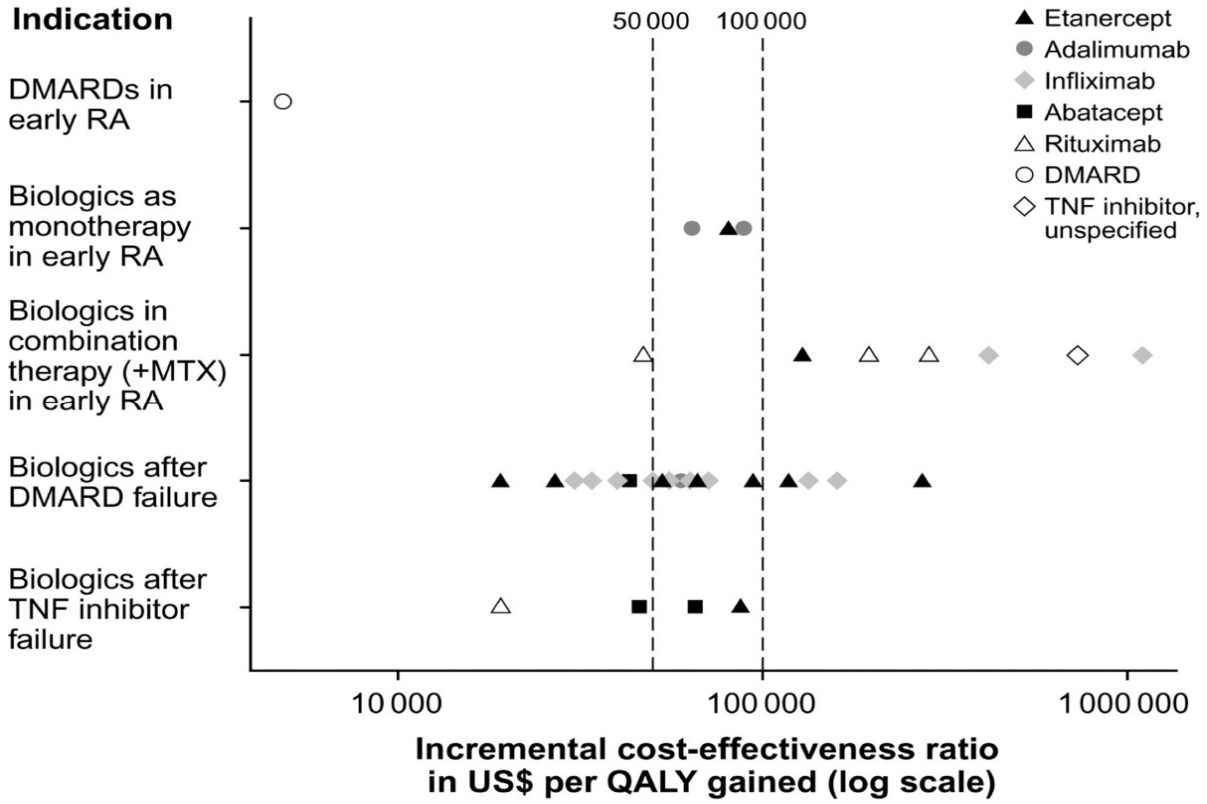
ICERs Favor Conventional DMARDs as First-line Therapy

Conventional DMARD vs	ICER ($/QALY)
	Payer Perspective
Adalimumab	$63,281 to $382,982/QALY
Infliximab	$71,936 to $1,464,344/QALY
Etanercept	$110,389 to $175,721/QALY
TNF inhibitors (class)	$139,744
Societal Perspective	
Infliximab	$141,827
TNF inhibitors (class)	$137,843

- These (and similar) findings lead most payers to require a trial of conventional DMARDs in treatment-naïve patients

Tsao NW, et al. *Best Pract Res Clin Rheumatol*. 2012;26:659-676.

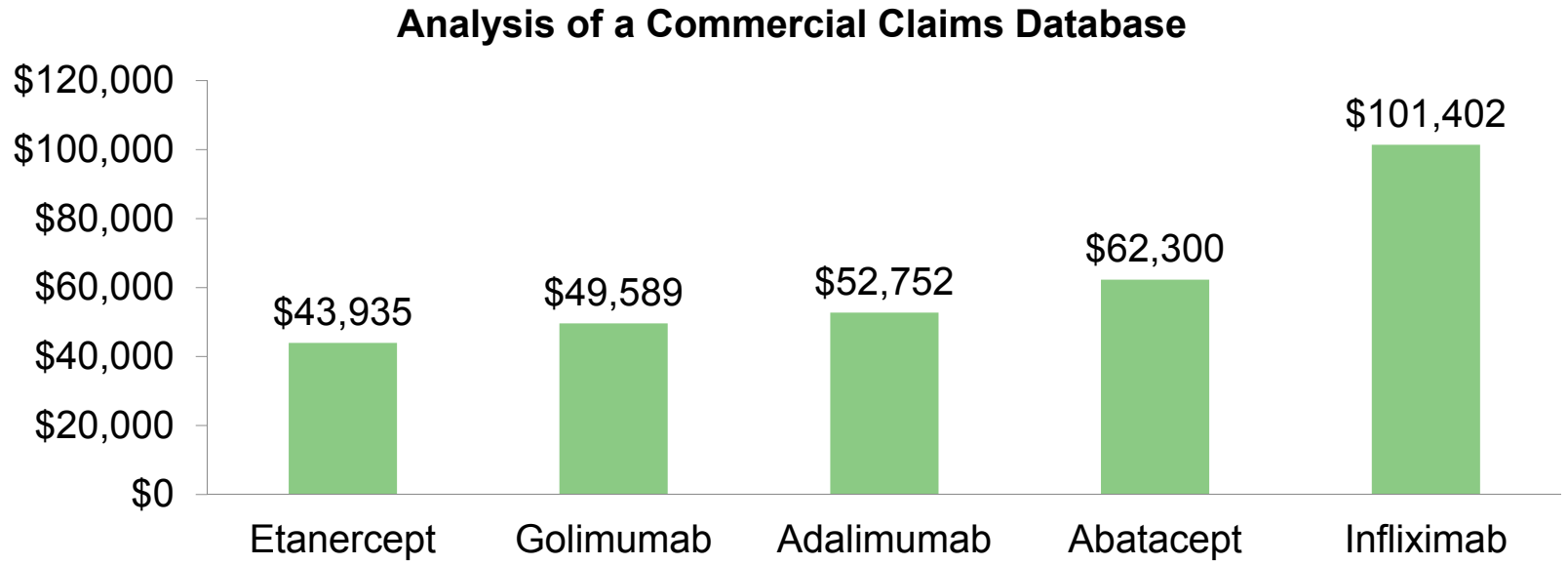
Biologics Begin to Be Cost-effective After Failure of a Conventional DMARD



- Early treatment should be with nonbiologic therapies
- Biologic treatments become cost effective after failure of therapy a conventional DMARD

Schoels M, et al. *Ann Rheum Dis*. 2010;69:995-1003.

Mean 1-Year Biologic Cost Per Effectively Treated Patient



- Effective treatment defined as meeting all 6 of the following criteria: 1) medication possession ratio ≥80% for SC biologics, or at least as many infusions as specified in the label for IV biologics; 2) no increase in biologic dose; 3) no switch in biologics; 4) no new nonbiologic DMARD; 5) no new or increased oral glucocorticoid treatment; and 6) no more than 1 glucocorticoid injection.

- Analysis of 5,474 RA patients (18-63 years) in the Optum Research Database who initiated biologic treatment between January 2007 - December 2010 and were continuously enrolled 6 months before through 12 months after the first claim for the biologic agent.

Curtis JR, et al. *J Manag Care Pharm*. 2015;21:318-328.

ICERs Favor Treatment with Biologics in DMARD-inadequate Responders

Sequential use/switching to another DMARD vs	ICER ($/QALY)
	Payer Perspective
Tocilizumab	$29,654/QALY
Abatacept	$58,376/QALY
Etanercept	$32,465 to $154,057/QALY
Adalimumab	$33,396 to $317,650/QALY
Infliximab	$37,225 to $313,144/QALY
TNFa inhibitors (class)	$53,802 to $291,531/QALY
Societal Perspective	
Infliximab	$59,924/QALY
Etanercept	$25,727 and $76,089/QALY
Adalimumab	$34,183/QALY
Tocilizumab	$29,707/QALY

Tsao NW, et al. *Best Pract Res Clin Rheumatol*. 2012;26:659-676.
Singh JA, et al. *Cochrane Database Syst Rev*. 2016;(5):CD012183.

Cost-effective Strategy in the Treatment of TNF Inhibitor IR Patients

- TNF inhibitors are frequently used sequentially in the case of a patient experiencing an inadequate response (IR) or intolerance to another TNF inhibitor
- Switching between biologic agents is common in medical practice
  - However, there is limited evidence that compares the overall costs and effectiveness of such a strategy

Beresniak A, et al. *Clin Exp Rheumatol*. 2013;31:400-408.

1st Line Use of Tofacitinib in Moderate-to-Severe RA Appears to be Cost-effective

- Cost-effectiveness evaluation of the JAK inhibitor tofacitinib for the treatment of Korean patients with RA who had an inadequate response to conventional DMARDs
- 1st line use of tofacitinib increased QALY gained vs standard-of-care, resulting in an ICER of KRW 13,228,910 (~$12,000) per QALY
- JAK inhibitor use also increased QALYs when incorporated as a 2nd, 3rd, or 4th line therapy
- Sensitivity analyses yielded ICERs in the range of KRW 6,995,719 (~$6,000) per QALY to KRW 37,450,109 (~$33,000) per QALY
- An increase in overall cost was observed in patients receiving a JAK inhibitor (attributable to increased lifetime drug costs)
- From a societal perspective, the inclusion of an oral JAK inhibitor as a treatment strategy for moderate-to-severe RA is cost-effective

KRW= Korean won (1 KRW = 0.00089 USD)

Lee MY, et al. *Clin Ther*. 2015;37:1662-1676.

Summary

- RA is associated with a significant clinical, psychosocial, and economic burden
- Conventional DMARDs are a more cost-effective first line treatment strategy than TNF inhibitors
- Treatment with a TNF inhibitors in patients refractory to previous DMARD therapies is more cost-effective vs switching to another conventional DMARD
- In TNF-IR patients, the alternative (non-TNF) biologics appear to be more cost-effective than switching to another anti-TNF agent
- Treatment with an oral JAK inhibitor for moderate-to-severe RA appears to be cost-effective across the treatment sequence

Rheumatoid Arthritis Comparative Analyses for Evidence-based Treatment and Benefit Design Decision-Making

Steven G. Avey, MS, RPh, FAMCP
Vice President, Specialty Clinical Programs
Medimpact Healthcare Systems, Inc.
San Diego, CA

In my lifetime…

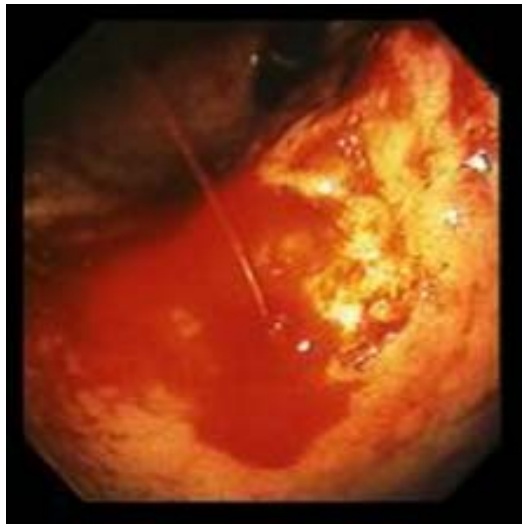
Graduated from pharmacy school in **1976**

What was the <u>standard therapy</u> for RA?

Drug of Choice for RA in 1976

Cost of therapy - Patient paid 100% = $50 to $100 per year

What did we do when patients had a GI Bleed?



No problem…

We put them on an antacid

2 tablespoonsful every 4 hours

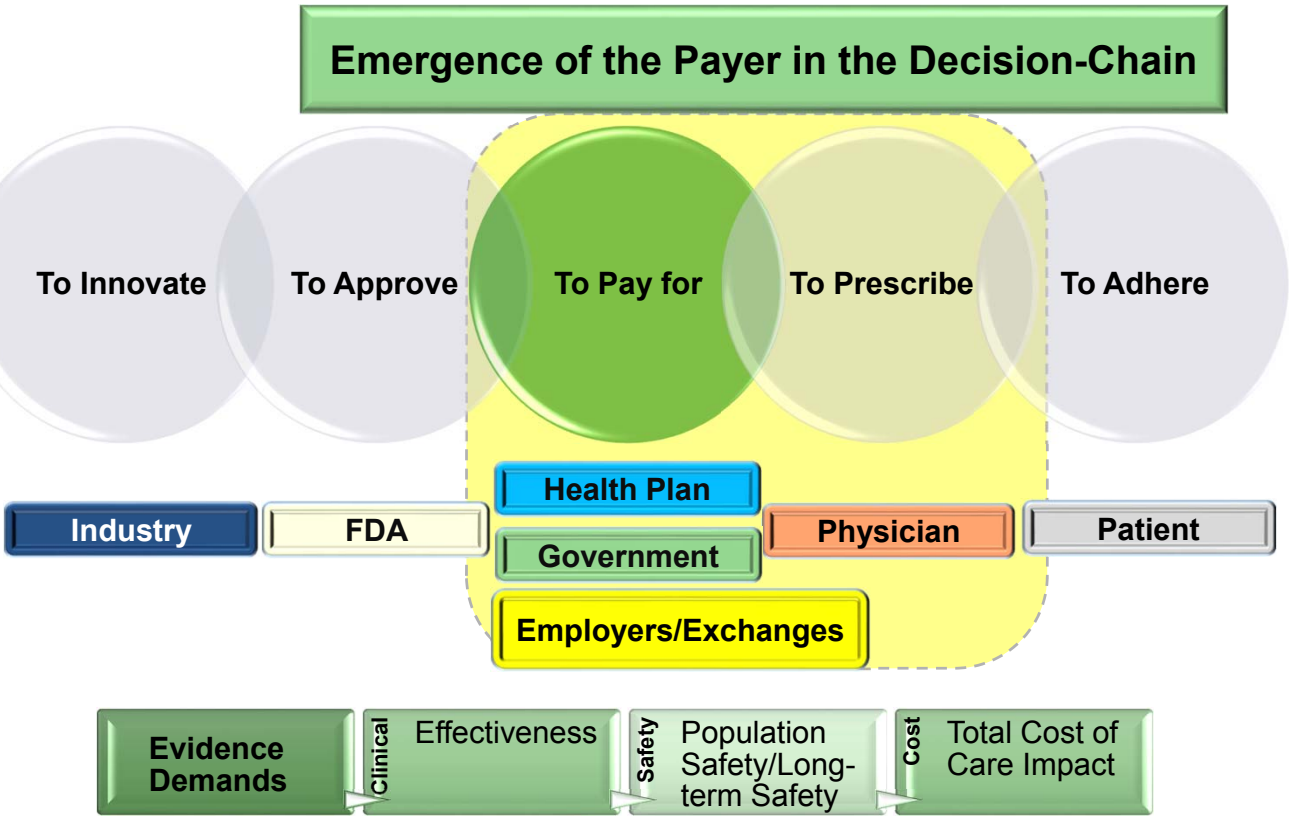
Patients purchased Maalox by the case!

The World Has Changed

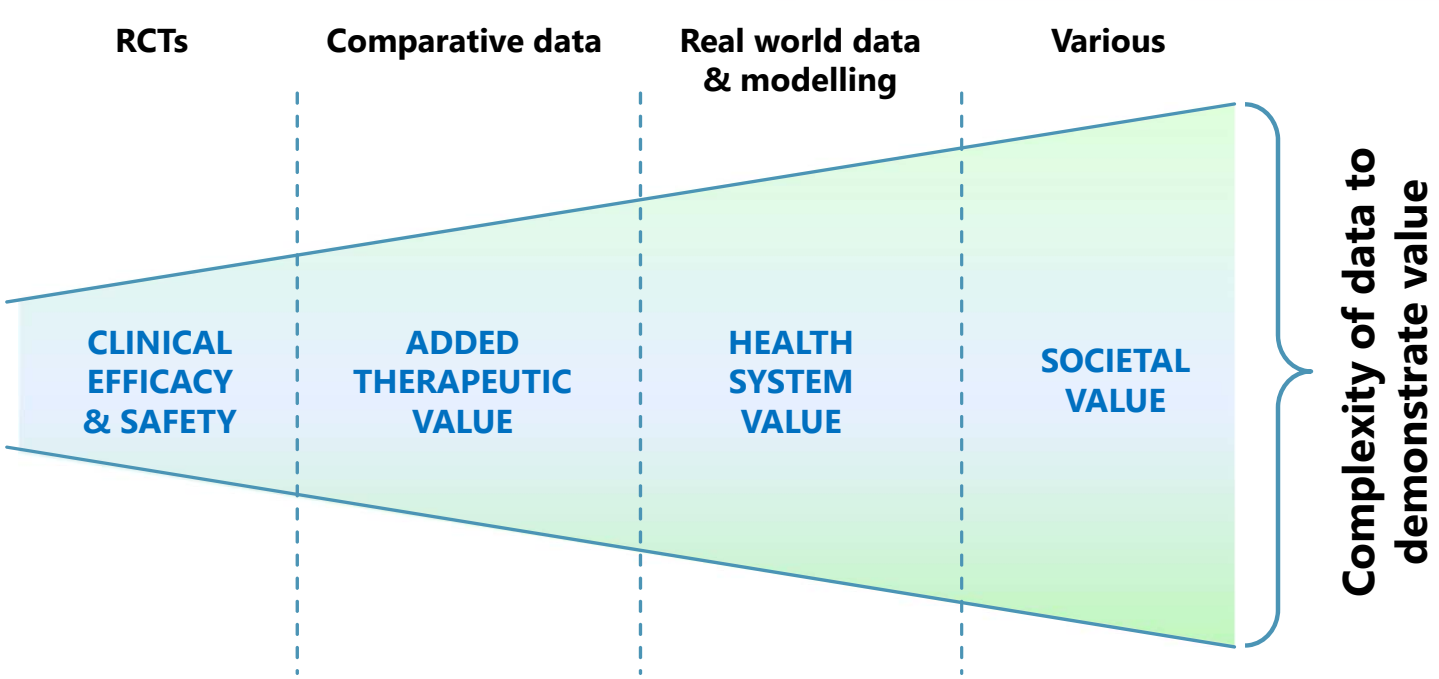
Agenda for 2016 RA Therapy

- New world / new therapies / new costs
- Real-world evidence
- Formulary decisions
- Contracting issues
- Where we go from here

Shifting Landscape



Emerging Approach – Value Based



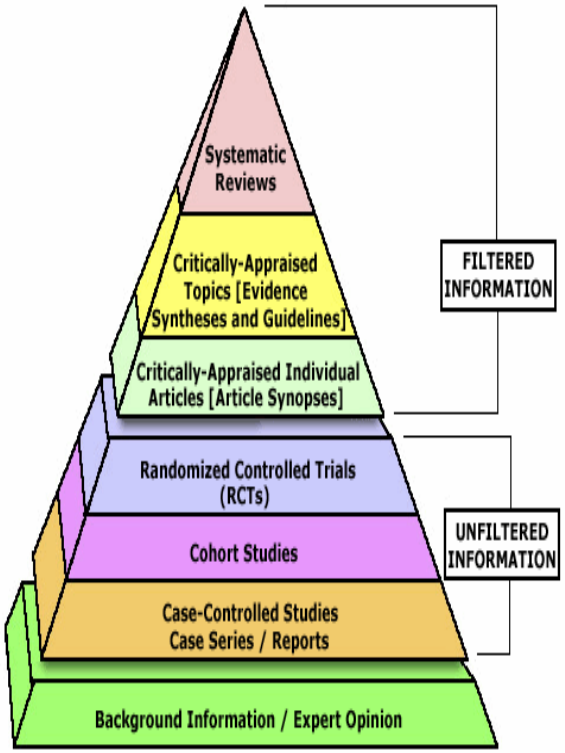
CER – Value in EBM Review of Medications

- Supports EBM approach
- Addresses key questions that formulary decision-makers need to consider regarding a medication
- Builds a foundation in developing a comprehensive EBM formulary drug review
- Tackles challenges in:
  - Reviewing and critically appraising large amounts of data
  - Analyzing several products in a class or across classes
- Identifies evidence gaps for future research
- Provides information for practical considerations

EBM Approach for Formulary Drug Review

What Information is Used?

Evidence Hierarchy



Trusted Sources - CER Systematic Reviews

- Cochrane Database of Systematic Reviews
- Agency for Healthcare Research & Quality (AHRQ)
- Drug Effectiveness Review Project (DERP)
- Centre for Reviews and Dissemination
- Database of Abstracts of Reviews of Effects

Trusted Sources are best known for:

- Rigorous, systematic methodology
- Transparency
- Auditing/critical appraisal of included research to base conclusions
- Systematic reviews that hold up to critical appraisal by external users

"CER Systematic Reviews are NOT just narrative reviews."

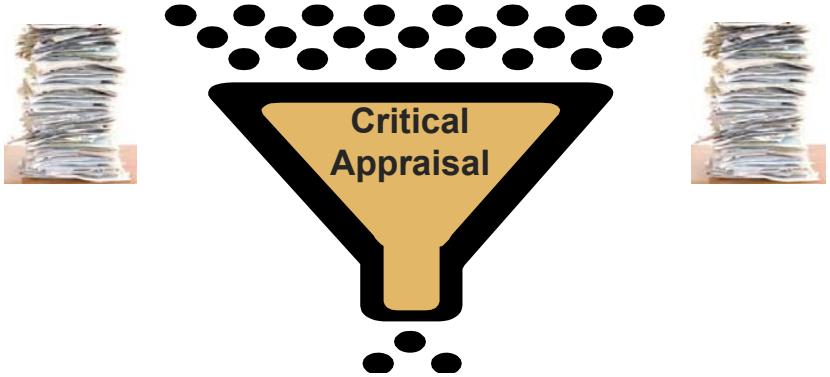
Formulary Drug Review

EBM Approach – Systematic Search

Key Questions (Formulary Issues)?

↓

Scientific Information (Clinical Trials)



Evidence Quality

↓

Evidence Synthesis

↙ **Superior** | ↓ | **Inferior** ↘

Insufficient Evidence

(80 – 90% of drugs reviewed)

P & T Formulary Decisions

EBM Formulary Decisions

Transparency in Weighing Practical Considerations

- **Scientific Evidence**
  - **High Confidence**
  - **Low Confidence**
- **Superior vs Similar**

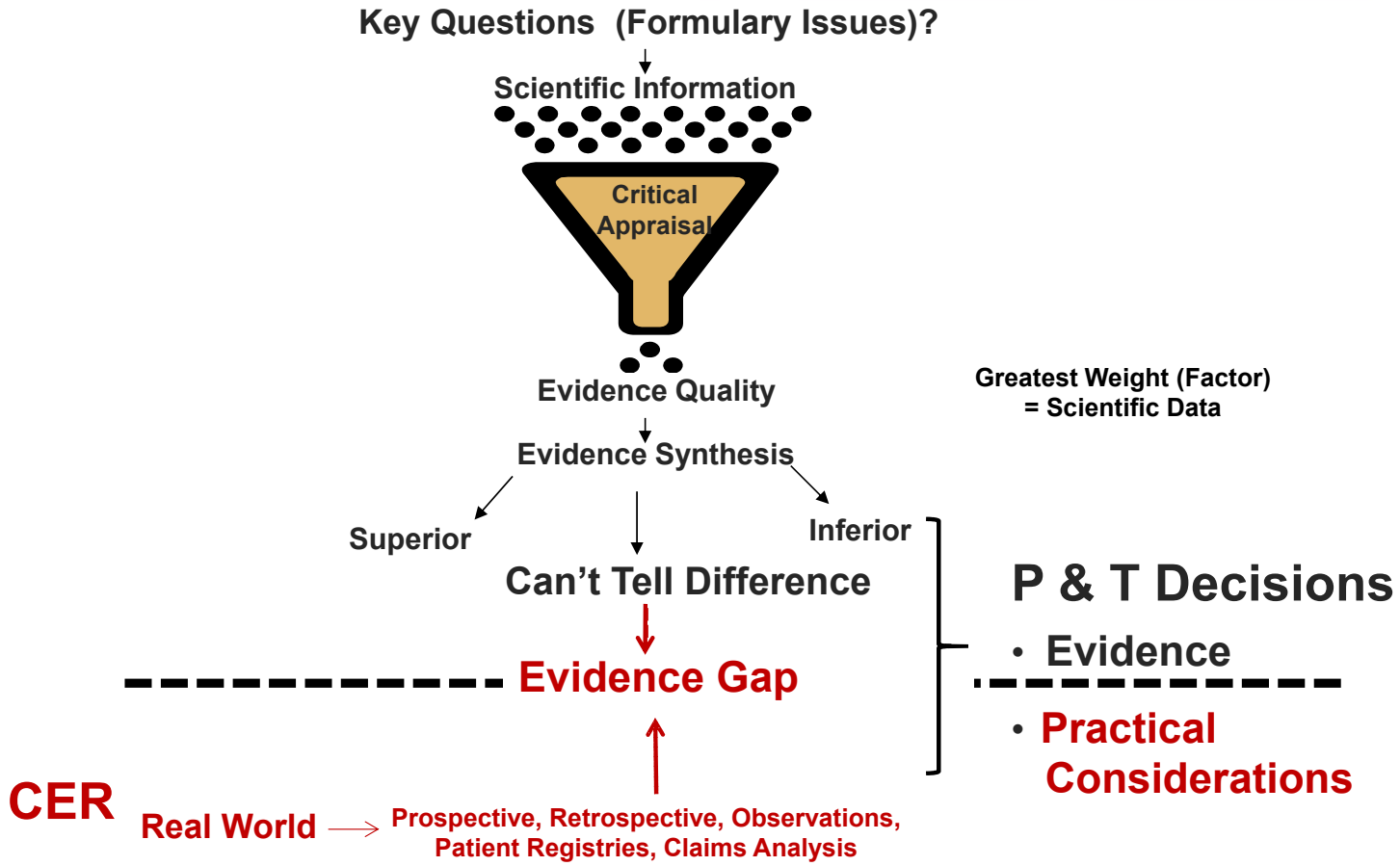
- **Practical Considerations***
  - **Other Options**
  - **Safety Signals/Harms**
  - **Disease Characteristics**
  - **Standard of Care**
  - **Impact on Clinical Burden**
  - **Cost**

*** May include real-world research**

Greatest Weight (Factor) = Scientific Data

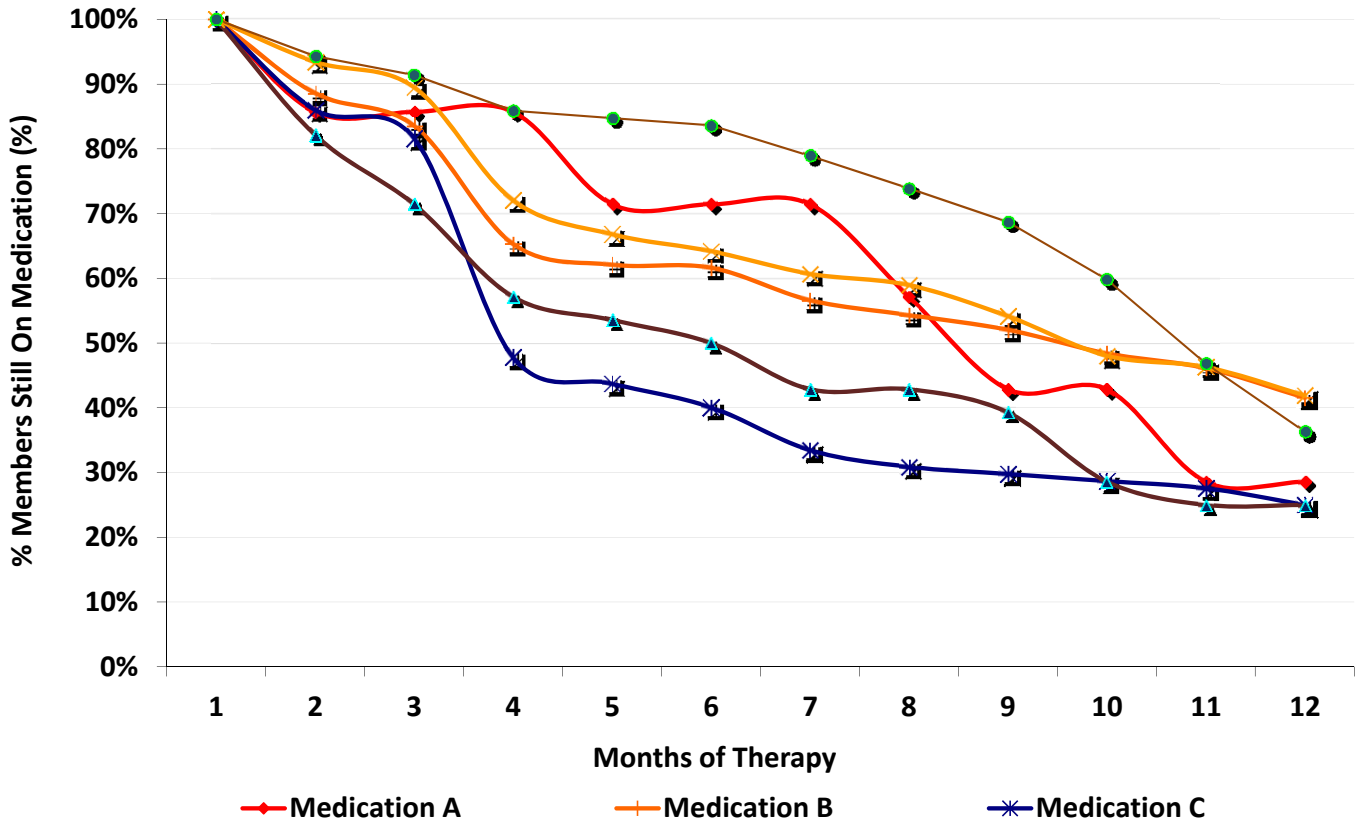
EBM Formulary Drug Review

Practical Use of CER to Address Evidence Gaps



CER Application – Impact on Clinical Burden

Medication Persistence



Internal Claims Database Analyses: RegenceRx 2005 – 2006.

CER Application: Outcomes/Overall Cost Rheumatologic Biologics

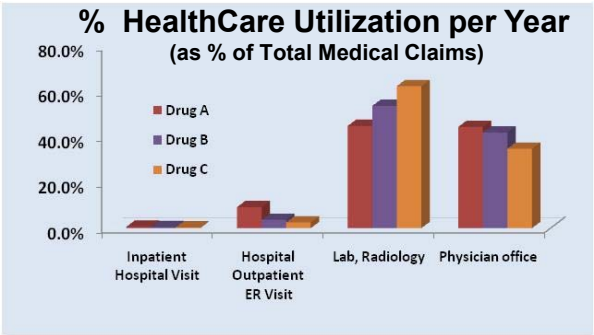
Clinical Trial Data

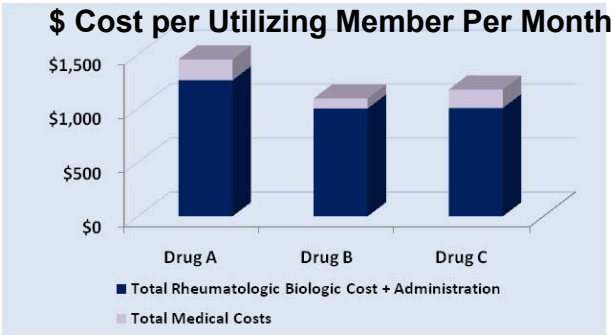
- Reliable quality evidence for biologics in rheumatologic conditions (rheumatoid arthritis, psoriatic arthritis/psoriasis, ankylosing spondylitis)
- Compared to standard treatments (ie, with or without methotrexate)
- Limited evidence for direct head-to-head comparison

Real-world CER

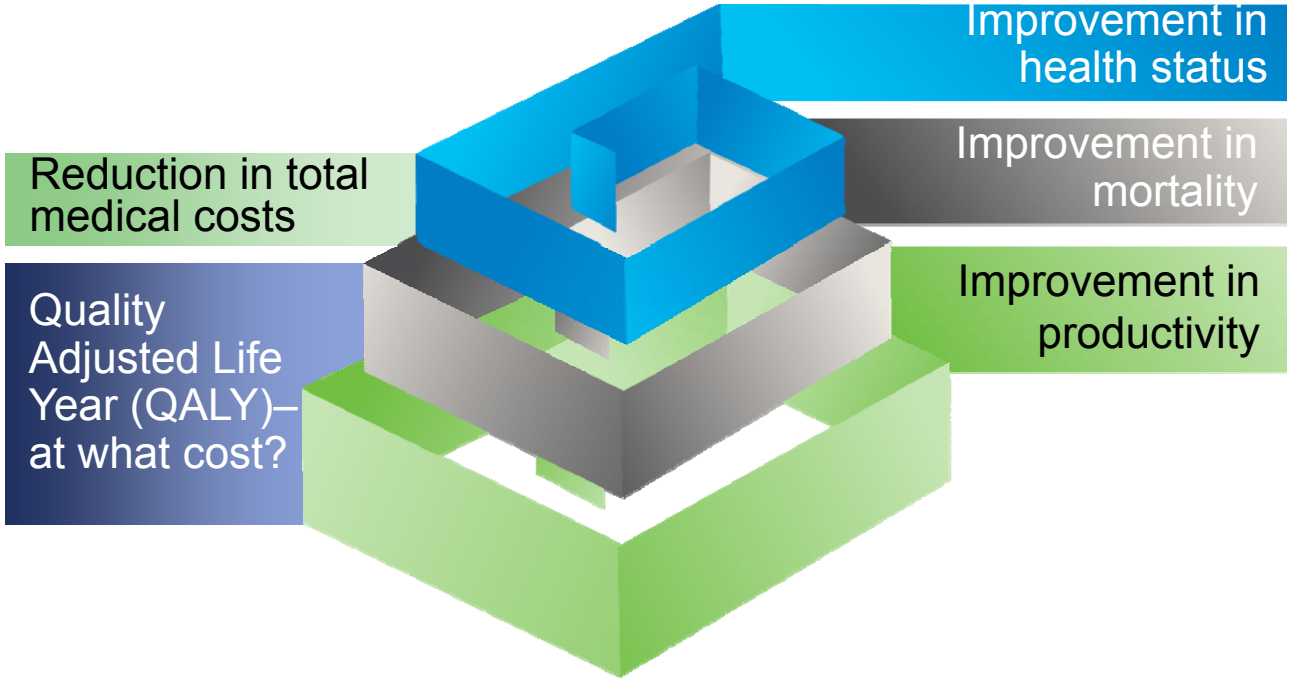
Compared to Drug A for rheumatologic conditions, Drugs B or C *associated* with:

- Fewer % outpatient hospital, ER visits
- Lower monthly medical costs per utilizing member
- Lower overall monthly costs per utilizing member (medical/drug/administration costs)





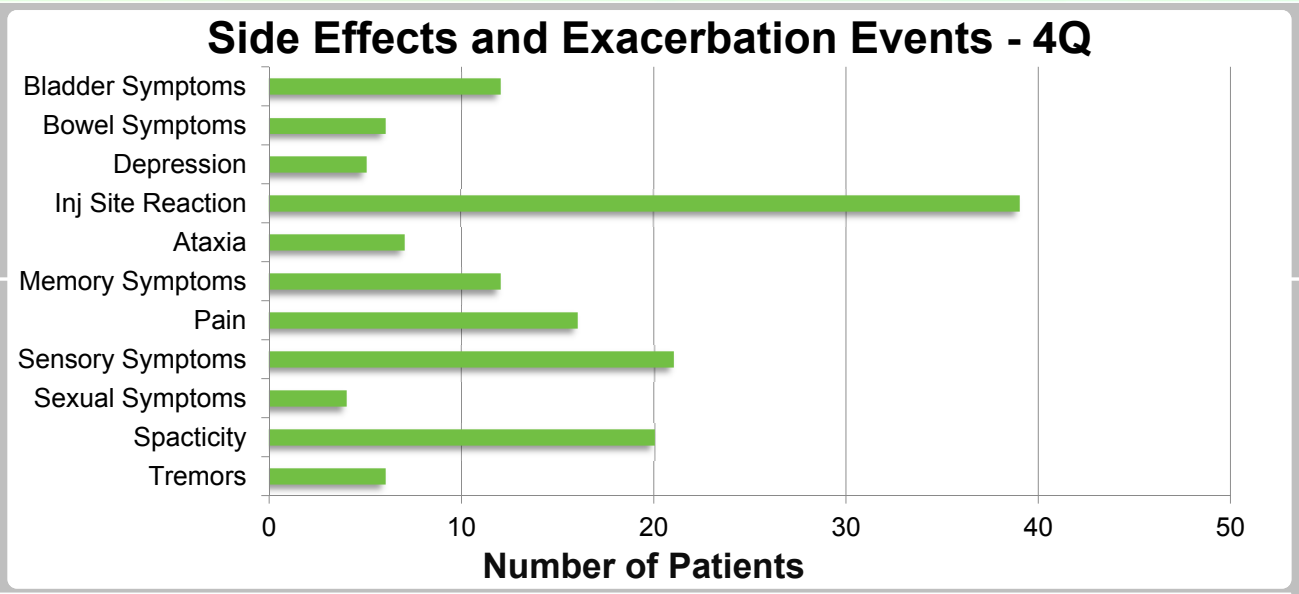
The Future of Value Calculations



Contracting and Evidence Issues

- Treatment failures
- Adherence failures
- Member failures
- Data and post marketing analyses

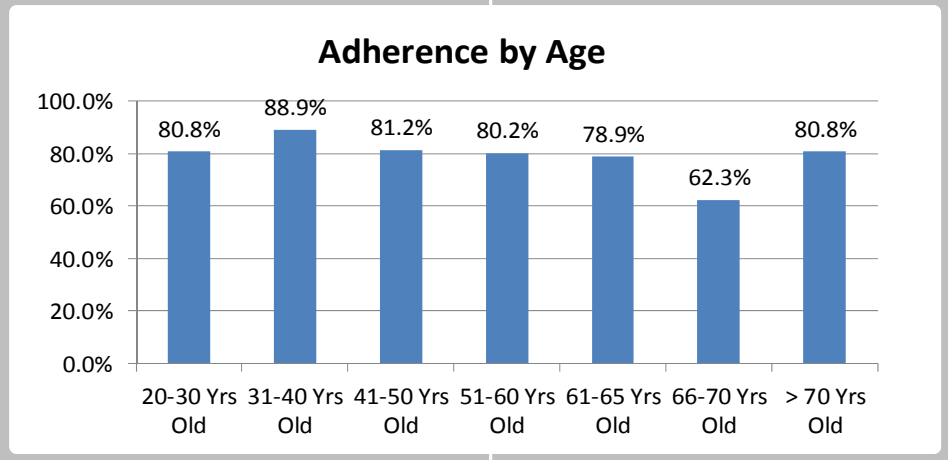
Reporting for Risk Sharing

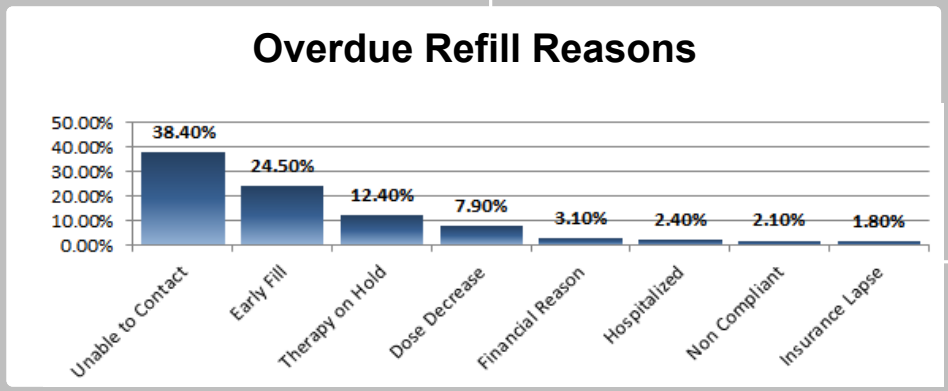


Such reports are available through an SP

- PhRMA commonly gets these reports
- We have a baseline from RCT data
- Compare 12 month data after product is approved

Risk-Sharing with an SP – Adherence





- Patients segmented for adherence by multiple parameters
- Target opportunities for adherence interventions
- Drill down on differences in adherence due to prescriber, drug, age, reported reasons for non-adherence, etc

New Risk-sharing for the Member

Adherence Contracts

- On the rise
- Increases member responsibility
- What happens with patients who are < 50% adherent?
- Advantages vs disadvantages

Potential Risk Arrangements with PhRMA

- Does post-marketing analysis compare to clinical trial data? Penalty or refund?
- Patient outcomes data will be required and agreed to
- Contracts already in place for adherence risk adjustment

Where Can We Go from Here?

- Determine better testing and outcomes assessments to determine patient health status
- Showcase advantages of treatment
- Better outcomes reporting on interventions and patient satisfaction
- Better collaboration between the PBM, the Specialty Pharmacy, and PhRMA