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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Inaugural National Conference

December 3 – 5, 2020

VIRTUAL CONFERENCE

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Rheumatoid Arthritis
New Treatments, New Approaches

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Disclosure

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Faculty Disclosures

Wendy Simmons, PA-C, DFAAPA

- Speakers Bureau: Abbvie, Amgen, Boehringer Ingelheim, Pfizer, Radius, UCB
- Advisory Boards: Amgen, Avion, BMS, Gilead, Janssen, Scipher

Objectives

- “Take Back to Clinic Tomorrow”
- Updated epidemiology, risk factors along with comorbidities for developing and worsening RA and where they fit in with conversations and treatment plans
- Understanding 4 stages of RA with importance of stepwise and logical therapy
- Updates in ACR, EULAR and Treat-to-Target Guidelines
- Utilizing these guidelines with managing FDA approved therapies for LDA and clinical remission
- Hot Topic JAK Generation vs TNF, What Generation are You?
- APP communication with RA patients for healthy outcomes

Epidemiology, Prevalence, Risks

- Over past 3 years significant decline in seropositive RA, same incidence of RA.
- Dr. Myasoedova, Mayo Clinic, Rochester, Minn., Rochester Epidemiology Project.
- Results from a population-based incidence study, 1985-204.
- Significant increase in RF-negative RA and decrease in RF-positive RA, in 2005-2014 compared to previous decades, using 1987 ACR criteria.
- Changing prevalence of environmental triggers, smoking obesity, others might have contributed.

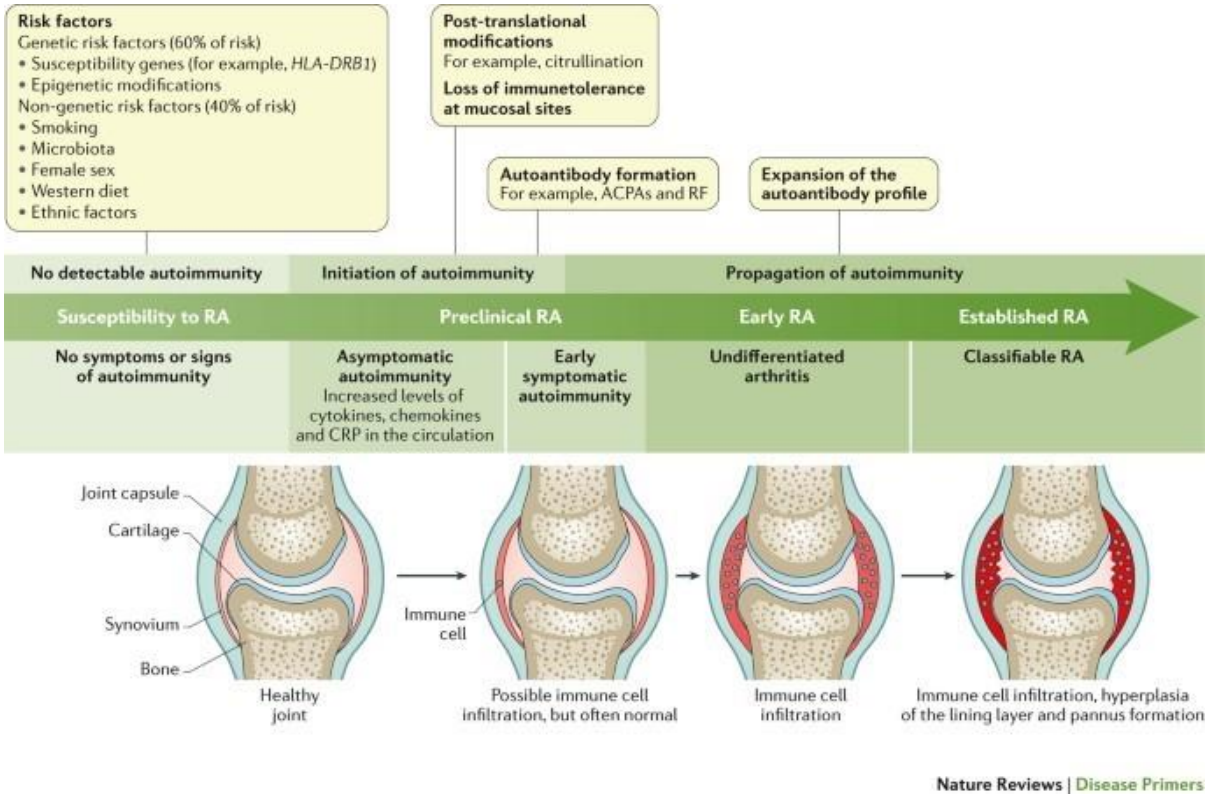
(Annuals of Rheumatic Dis. 2020 Feb 17)

Epidemiology, Prevalence, Risks (cont'd)

- Female 2-3 times male population
- Age onset any age, highest in 60's
- Genetic predisposition, HLA genotype, combined with environmental triggers
- Tobacco use, obesity, diet, stress, dental disease
- Comorbidities, need to be identified early, address lifestyle changes

pubmed.ncbi.nim.nih.gov. Is the epidemiology of rheumatoid arthritis changing? By E. Myasoedova 2020.
Ann Rheum Dis. 2020 Feb 17. Pil:ann rheumdis-2019-216694.

4 Stages of RA Nature Review



Smolen. Rheumatoid Arthritis. *Nature Reviews Disease Primers.* 2018.

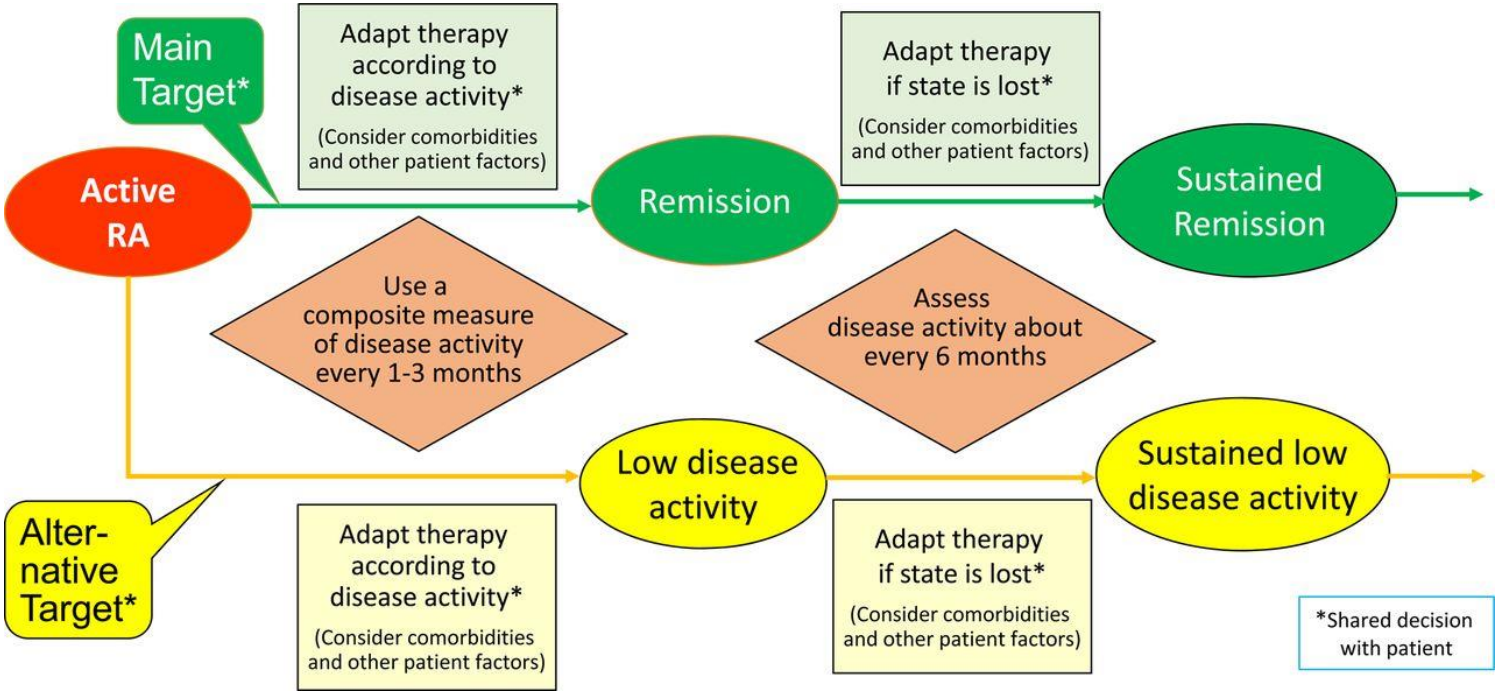
Early RA

- Aggressive treatment, treat-to-target, goals of LDA and clinical remission
- Methotrexate continues to be anchor of care
- Address comorbidities, risk factors, systemic disease

FDA Approved DMARDs for RA – 2020

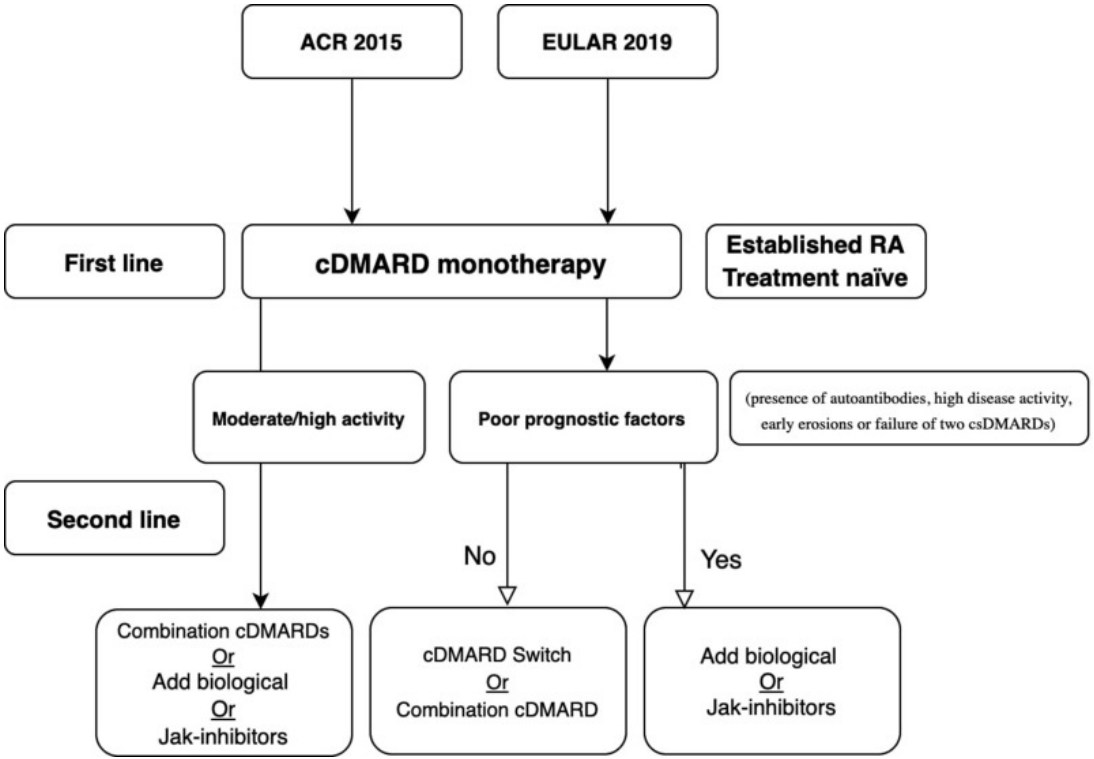
- Conventional
  - Hydroxychloroquine
  - Sulfasalazine, methotrexate, leflunomide
- Targeted
  - JAK Inhibitors
  - Tofacitinib – JAK3/JAK1, JAK2
  - Baricitinib – JAK1/JAK2
  - Upadacitinib – JAK1
- Biologic DMARDs
  - TNF inhibitor etanercept, adalimumab, certolizumab pegol, inflixamib, golimumab
  - IL-1 anakinra
  - IL-6 tocilizumab, sarilumab
  - T cell inhibitor: abaracept
  - B cell inhibitor rituximab
- Biosimilars infliximab, etanercept, adalimumab, rituximab

Treat-to-Target



Smolen. Annuals of the Rheumatic Diseases. *The BMJ*. 2014;
Smolen. Treating rheumatoid arthritis to target 2014 update of the recommendations of an international task force. 2016. ard.bmj.com.

ACR EULAR



Chaplin. Summary of the new EULAR rheumatoid arthritis guidelines. 2020. wchh.online library.wiley.com;
EULAR definition of difficult to treat rheumatoid arthritis. Ard.bmj.com 20.

New Guideline Changes

- ACR Guidelines 2015, ACR changes (in print 2021), methotrexate, steroids
- EULAR publishes new difficult-to-treat RA
- Treat-to-target updates
- Utilization of ultrasound

Chaplin. Summary of the new EULAR rheumatoid arthritis guidelines. 2020. wchh.online library.wiley.com;
EULAR definition of difficult to treat rheumatoid arthritis. Ard.bmj.com 20;
JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the Emerging Clinical Data. www.ncbi.nim.nih.gov.

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Sustained Remission on Combination Therapy – What to Do Now?

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ABSTRACT NUMBER: 0939

Maintenance of Remission After Withdrawal of Etanercept or Methotrexate in Patients with Rheumatoid Arthritis in Sustained Remission on Combination Therapy: Results from a Randomized, Double-blind, Controlled Trial

Jeffrey R Curtis[1], Paul Emery[2], Elaine Karis[3], Boulos Haraoui[4], Vivian Bykerk[5], Priscilla Yen[3], Gregory Kricorian[6] and James Chung[3], [1]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK, Leeds, United Kingdom, [3]Amgen, Inc., Thousand Oaks, CA, [4]Rheumatology Institute of Montréal, Montreal, Canada, [5]Hospital for Special Surgery, New York, NY, [6]Amgen Inc., Thousand Oaks, CA

Background / Purpose

Maintenance of Remission After Withdrawal of Etanercept or Methotrxate in Patients with Rheumatoid Arthritis in Sustained Remission on Combination Therapy: Results from a Randomized, Double-blind, Controlled Trial

- Rheumatoid arthritis (RA) patients in remission on combination (Combo) therapy of methotrexate (MTX) + etanercept (ETN) face ongoing medication burden and long-term safety/tolerability concerns related to continuing therapies.
- Reducing therapy has been studied, but whether patients could discontinue either MTX or ETN and maintain remission on monotherapy has not been rigorously tested.
- This study compared withdrawing either MTX or ETN on remission maintenance in RA patients who had been in sustained, stringent remission while on Combo.

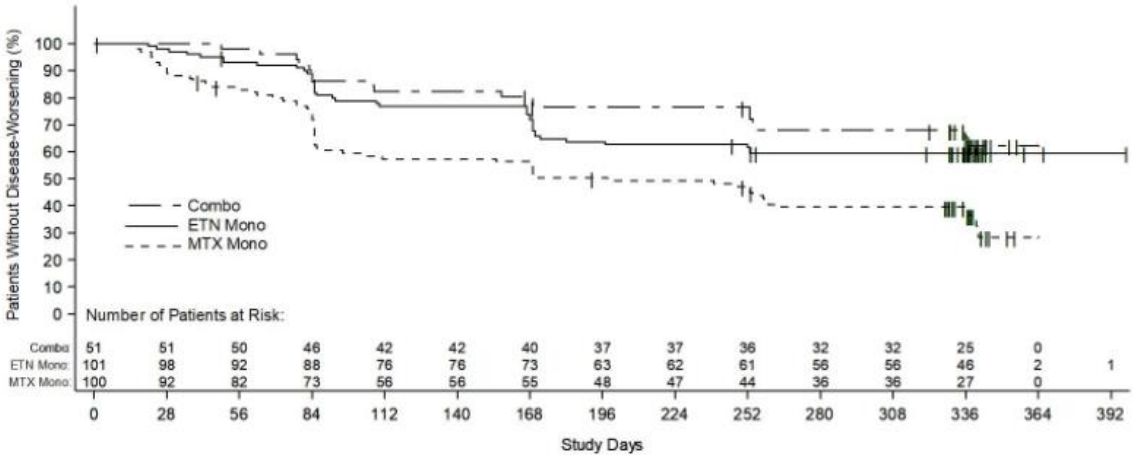
Methods

- The Study of ETN And MTX in RA (SEAM-RA) enrolled adult RA patients on ETN 50 mg/week + MTX 10-25 mg/week who met ACR/EULAR remission criteria (SDAI) score </= 3.3 in a 24-week, open label period.
- After 24 weeks, pts remaining in remission entered 48-week double-blind period and were randomized to: (1) withdrawal of ETN (MTX mono); (2) withdrawal of MTX (ETN mono); or (3) continue Combo.
- Patients with disease- worsening (DW) defined as SDAI > 11 or > 3.3 and </= 11 received Combo rescue therapy (Combo arm continued Combo therapy) and were considered non-responders.
- Endpoints included proportion of pts in SDAI remission without DW at week 48 in the ETN mono vs MTX mono arms (primary) and in the Combo vs MTX mono arms (secondary).
- Other secondary endpoints included time to DW and time to recapture SDAI remission in pts needing rescue therapy.

Results

- 371 patients, 24-week, open-label period, 253 (68.2%) remained in remission, randomized to double-blind period (101 MTX mono, 101 ETN mono, 51 (Combo).
- Baseline values similar in all arms: mean (SD) age 55.6 (12.2) years, RA duration 10.3 (7.8) years, MTX dose 16.3 (4.7) mg/week, SDAI score 1.3 (1.2).
- Week 48, SDAI remission was maintained by significantly more pts on ETN mono vs MTX mono (49.5% vs 28.7%; P=0.004) and by more pts on Combo vs MTX mono (52.9% vs 28.7%; P=0.006).
- Time to DW was shorter with MTX mono compared with ETN mono or Combo (P<0.001 for both comparisons; Fig 1).
- Pts with DW treated with Combo rescue therapy, the cumulative percentage who recaptured SDAI remission by end of study was 71%, 75%, and 80% in the MTX mono, ETN mono, and Combo arms, respectively.
- Time to recapture SDAI remission after initiating rescue therapy was similar in all 3 treatment arms.
- No new safety signals were reported.

Figure 1. Kaplan-Meier Curves of Time to Disease-Worsening (Primary Analysis Set)



	MTX Mono (N = 101)	ETN Mono (N = 101)	Combo (N = 51)
Days to Disease-Worsening, Median (95% CI)	198 (96, 263)	NE (253, NE) P<0.001*	NE (336, NE) P<0.001*

*P-values are nominal and compare the ETN-containing arms with the MTX mono arm using a log-rank test. One patient in the MTX arm discontinued at study day 0, and was thus no longer at risk and was censored.
CI, confidence interval; Combo, combination; ETN, etanercept; mono, monotherapy; MTX, methotrexate; NE, not estimable.

Conclusion

- In pts in remission on Combo who then withdrew either MTX or ETN, this study showed that ETN mono was superior to MTX mono in maintaining remission.
- Similar proportions of pts maintained remission with ETN mono as with Combo.
- Majority of pts who received rescue therapy recaptured remission.
- Similar proportions of pts who received rescue therapy recaptured remission.
- For pts and physicians seeking to reduce treatment burden, these data inform decision-making on therapy withdrawal in well-controlled RA pts.

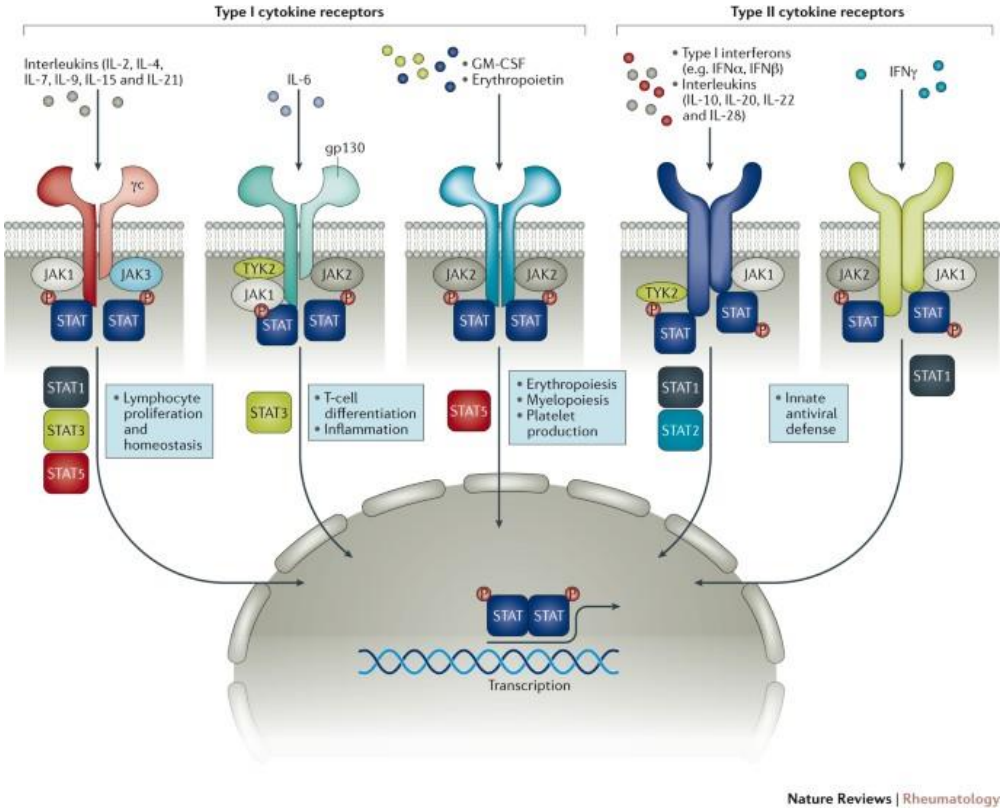
FDA Approved New Treatments – JAK “Generation”

- Tofacitinib JAK1/JAK3, 2008, baricitinib JAK1/JAK2, 2012, upadacitimib Jak 1 2019
- Small molecules, oral biologic option for RA patients with inadequate response to MTX
- Comparable efficacy to TNF inhibitors (ACR response rates and DAS28 scores)
- Rapid onset of action, efficacy as soon as 2 weeks and sustained beyond 3 months, early reduction of pain, demonstrating slow radiographic progression
- ACR 2015 and EULAR 2019 guidelines consider JAK inhibitors 2nd line treatment in moderate or high disease activity refractory to MTX therapy
- Upadacitinib + MTX combination demonstrates highest ACR response rates among available JAK inhibitors

JAK Inhibitors Side Effects and Safety

- Most common AE infections, respiratory, UTI, similar to bDMARDs.
- Herpes Zoster higher than bDMARDs, rare disseminated cases, vaccinate.
- Venous thromboembolism risk with higher doses of tofacitinib than approved for RA, get history of prior VTE before considering JAK
- No increased risk of malignancies
- Lipid monitoring, chronic inflammation in RA causes false low levels of LDL, JAKs and bDMARDs correct low levels of LDL without negatively impacting cardiovascular risk
- Monitor cytopenia, particularity neutropenia, lymphopenia

JAK Mechanism of Action



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ABSTRACT NUMBER: 0797

Comparison of the Efficacy and Safety of Janus Kinase Inhibitors and DMARDs in Patients with Active Rheumatoid Arthritis: A Bayesian Network Meta-Analysis

Adela Castro[1], Jesus Diaz[2] and Guillermo Quiceno[3], [1]UT Southwestern, Dallas, TX, [2]Universidad de los Andes, Dallas, TX, [3]UT Southwestern Medical Center, Dallas, TX

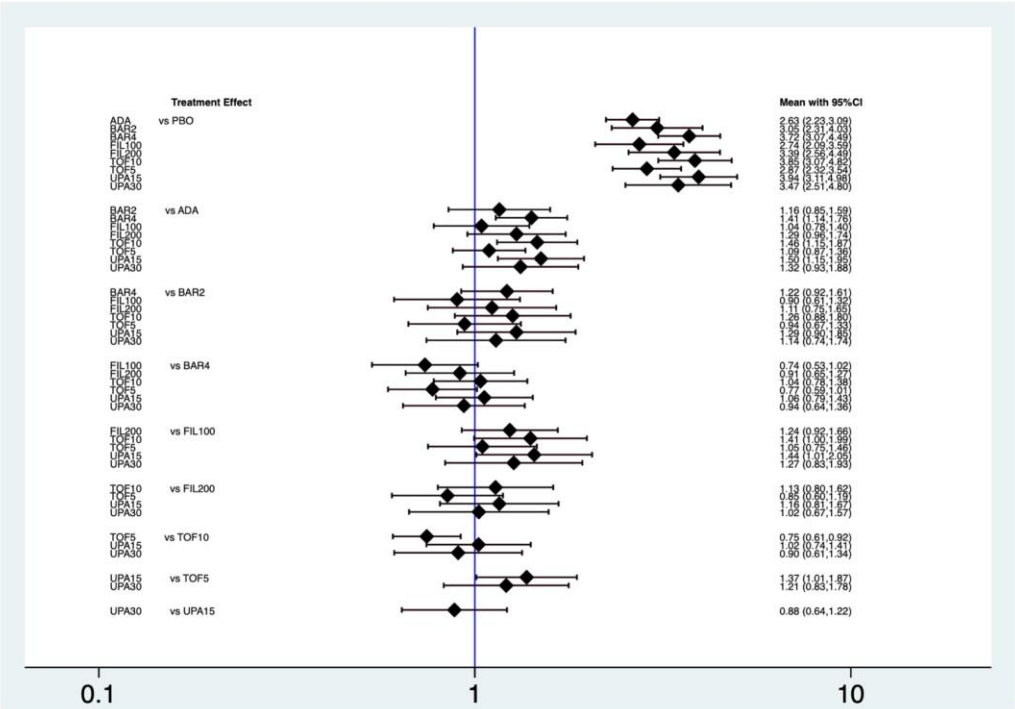
Background / Purpose

- Janus Kinase (JAK) inhibitors have shown long term benefits with active RA with inadequate response to conventional or biologic DMARDs.
- Due to lack of head-to-head comparison trials, the relative efficacy and safety of JAK inhibitors remains unclear.
- Consequently, previous network meta-analysis had assessed the relative efficacy and safety of JAK inhibitors but were restricted to studies with adalimumab.
- Purpose of study to investigate relative efficacy and safety of tofacitinib, baricitinib, upadacitinib, and filgotinib.

Methods

- Bayesian random-effects network meta-analysis was performed to combine the direct and indirect evidence from randomized controlled trials (RCTs) reporting efficacy and safety outcomes of tofacitinib + MTX, baricitinib + MTX, upadacitinib + MTX, filgotinib + MTX in patients with active RA despite treatment with conventional or biologic DMARDs.

Results



- Twenty RCTs including 13,178 patients met inclusion criteria.
- 45 pairwise comparisons including 18 direct comparisons of 10 interventions.
- ACR 20 response rate significantly higher for all intervention groups than placebo (fig 1).

UPA15 = upadacitinib 15mg + MTX; TOF10 = tofacitinib 10mg + MTX; BAR4 = baricitinib 4mg + MTX;
UPA30 = upadacitinib 30mg + MTX; FIL200 = Filgotinib 200mg + MTX; BAR2 = baricitinib 2mg + MTX;
TOF5 = tofacitinib 5mg + MTX; FIL100 = filgotinib 100mg + MTX; ADA = adalimumab + MTX; PBO = placebo + MTX.

Results Continued

- Ranking probability based on surface under the cumulative ranking curve (SUCRA) indicated upadacitinib 15 mg + MTX, tofacitinib 10 mg + MTX, and baricitinib 4 mg + MTX had highest probability of being the best treatment in terms of ACR 20 response rate.
- Followed by upadacitinib 30 mg + MTX, filgotinib 200 mg + MTX, baricitinib 2 mg + MTX, tofacitinib 5 mg + MTX, filgotinib 100 mg + MTX, adalimumab + MTX and placebo + MTX.

Results Continued

- The SUCRAs for ACR50 indicated that upadacitinib 30 mg + MTX and upadacitinib 15 mg had highest probability of being the best treatment.
- Safety based on number of severe adverse events did not differ significantly among the 10 interventions within 12 weeks suggesting comparable safety among the different regimes and placebo.
- Observed an increased risk of herpes zoster infection in group of tofacitinib 10 mg + MTX and baricitinib 4 mg + MTX in comparison with placebo group.

Network League of Estimated Effects of ACR20 and Herpes Zoster Infections

UPA15	5.38 (0.81,35.88)	1.54 (0.46,5.10)	1.92 (0.57,6.45)	0.98 (0.19,5.03)	1.03 (0.20,5.42)	1.77 (0.43,7.36)	1.33 (0.25,7.00)	1.12 (0.36,3.52)	1.54 (0.58,4.09)
1.02 (0.74,1.41)	**TOF10**	3.50 (0.62,19.73)	2.81 (0.36,21.68)	5.52 (0.69,43.85)	5.23 (0.64,42.59)	3.04 (0.59,15.63)	7.16 (0.89,57.75)	4.80 (0.95,24.21)	**8.27 (1.56,43.76)**
1.06 (0.79,1.43)	1.04 (0.78,1.38)	**BAR4**	1.25 (0.30,5.13)	1.58 (0.36,6.87)	1.49 (0.41,5.43)	1.15 (0.36,3.65)	2.05 (0.46,9.11)	1.37 (0.65,2.91)	**2.36 (1.10,5.10)**
1.13 (0.82,1.56)	1.11 (0.75,1.64)	1.07 (0.74,1.55)	**UPA30**	1.97 (0.32,11.91)	1.86 (0.30,11.49)	1.08 (0.21,5.48)	2.55 (0.41,15.75)	1.71 (0.43,6.84)	2.95 (0.88,9.91)
1.16 (0.81,1.67)	1.13 (0.80,1.62)	1.10 (0.79,1.53)	1.02 (0.67,1.57)	**FIL200**	1.06 (0.16,6.91)	1.82 (0.36,9.29)	1.30 (0.34,4.90)	1.15 (0.29,4.59)	1.50 (0.39,5.78)
1.29 (0.90,1.85)	1.26 (0.88,1.80)	1.22 (0.92,1.61)	1.14 (0.74,1.74)	1.11 (0.75,1.65)	**BAR2**	1.72 (0.32,9.13)	1.37 (0.21,9.12)	1.09 (0.26,4.55)	1.58 (0.40,6.22)
1.37 (1.01,1.87)	**1.34 (1.09,1.65)**	1.30 (0.99,1.70)	1.21 (0.83,1.78)	1.18 (0.84,1.66)	1.06 (0.75,1.50)	**TOF5**	2.36 (0.45,12.27)	1.58 (0.64,3.92)	2.72 (0.89,8.36)
1.44 (1.01,2.05)	1.41 (1.00,1.99)	1.36 (0.98,1.88)	1.27 (0.83,1.93)	1.24 (0.92,1.66)	1.12 (0.76,1.64)	1.05 (0.75,1.46)	**FIL100**	1.49 (0.37,6.07)	1.16 (0.29,4.57)
1.50 (1.15,1.95)	**1.46 (1.15,1.87)**	**1.41 (1.14,1.76)**	1.32 (0.93,1.88)	1.29 (0.96,1.74)	1.16 (0.85,1.59)	1.09 (0.87,1.36)	1.04 (0.78,1.40)	**ADA**	1.72 (0.82,3.65)
3.94 (3.11,4.98)	**3.85 (3.07,4.82)**	**3.72 (3.07,4.49)**	**3.47 (2.51,4.80)**	**3.39 (2.56,4.49)**	**3.05 (2.31,4.03)**	**2.87 (2.32,3.54)**	**2.74 (2.09,3.59)**	**2.63 (2.23,3.09)**	**PBO**

ACR20	Intervention	HZ

Drugs are reported in order of ACR20 ranking according to SUCRAs. Comparisons should be read from left to right. The efficacy (ACR20) and safety (herpes zoster infection) estimate is located at the intersection of the column-defining treatment. Significant results are in bold and underlined.

Conclusion

- In patients with active RA with inadequate response to conventional or biologic DMARDs the JAK inhibitors are an effective and safe alternate therapy.
- The two with the best relative efficacy were upadacitinib 15mg/30mg and baricitanib 4 mg.
- In terms of serious infectious events, there was an increase of herpes zoster infections with tofacitinib and baricitanib 4 mg.

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ABSTRACT NUMBER: 0135

Understanding the Rheumatologist-Patient Relationship in Treating Rheumatoid Arthritis

Beth Schneider[1] and Eric Peacock[1], [1]MyHealthTeams, San Francisco, CA

Background / Purpose

- Understanding patient satisfaction with their rheumatologist and the drivers of satisfaction is crucial to improving doctor-patient interactions, helping patients get on the right treatment path to help slow progression and improving health outcomes overall.

Methods

- In January 2020 an email invitation to an online survey was sent to US members of myRAteam, a social network of over 122,000 members.
- In total, 374 US members completed the 21-question survey regarding the HCP-patient experience.

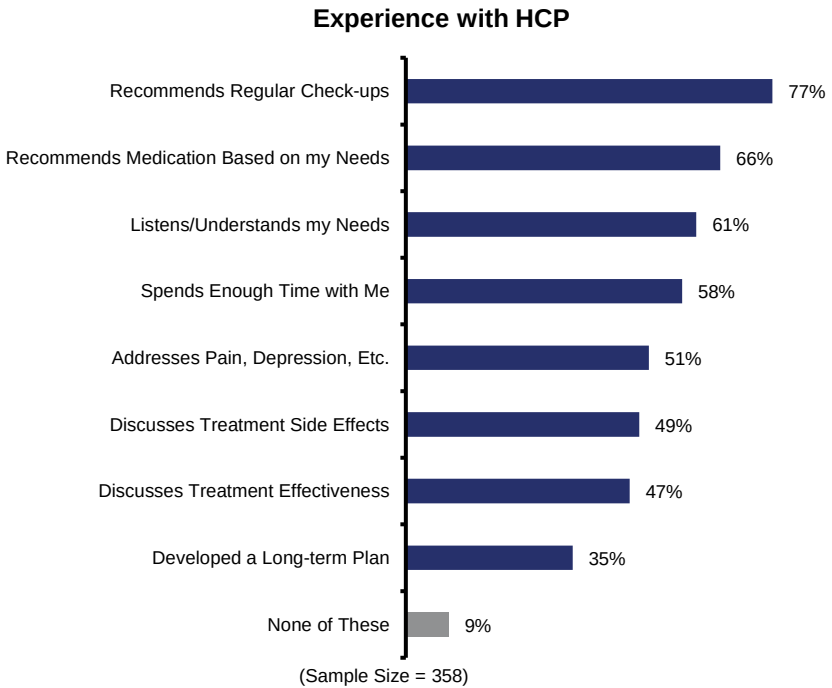
Results

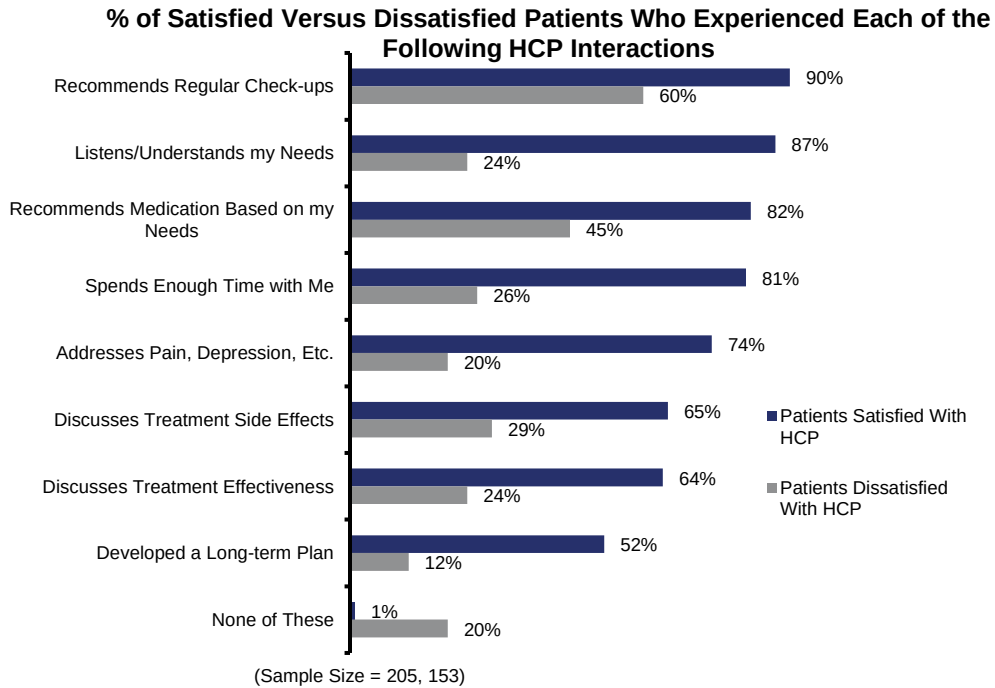
- Over half of RA patients surveyed are satisfied with their HCP (57%) and 78% feel they can have meaningful conversations.
- Majority feel HCP doing good job of recommending regular follow up (77%) and medications (66%) based on patients' unique needs.
- Slightly less than 2/3 feels their doctor listens to them and truly understands what they are going through (615) or spends enough time with them (58%).
- Biggest obstacles to managing RA are pain (80%), relentless fatigue (72%), depression/anxiety (51%0, only 51% of patients feel HCP addresses these symptoms.
- Only 37% are satisfied with current treatment and 49% feel HCP has developed a long-term plan for treating this progressive disease.

Conclusion

- Understanding the needs of RA patients provides significant opportunities for rheumatologists to better support and educate patients.
- Includes offering stronger recommendations on treatment path based on patient’s specific needs and goals, and specific information on diet/exercise approaches.
- Also means listening to patient concerns and addressing the mental health aspects of RA including pain, depression and fatigue, and not just disease progression.

Experience With HCP





Schneider B, Peacock E. Understanding the Rheumatologist-Patient Relationship in Treating Rheumatoid Arthritis [abstract]. *Arthritis Rheumatol.* 2020; 72 (suppl 10). https://acrabstracts.org/abstract/understanding-the-rheumatologist-patient-relationship-in-treating-rheumatoid-arthritis/.

Summary

- Rheumatoid Arthritis, chronic inflammatory destructive systemic disease
- Address patient's comorbidities/lifestyle early on and subsequent office visits
- New ACR/EULAR guidelines, support use of new therapies with use of JAK inhibitors, safely treating patients in a stepwise fashion, logically with monitoring, to achieve maximum efficacy
- Important we communicate with our patients to help achieve goals of LDA and clinical remission
- APP's trained to pivot well, listen, and have compassion and empathy

References

- pubmed.ncbi.nim.nih.gov Is the epidemiology of rheumatoid arthritis changing? By E. Myasoedova 2020 Ann Rheum Dis. 2020 Feb 17. Pil:ann rheumdis-2019-216694
- Rheumatoid Arthritis Nature Review Disease Primers Smolen 2018
- Annuals of the Rheumatic Diseases The BMJ Smolen 2014
- Castro A, Diaz J, Quiceno G. Comparison of the Efficacy and Safety of Janus Kinase Inhibitors and DMARDs in Patients with Active Rheumatoid Arthritis: A Bayesian Network Meta-Analysis [abstract]. Arthritis Rheumatol. 2020; 72 (suppl 10). https://acrabstracts.org/abstract/comparison-of-the-efficacy-and-safety-of-janus-kinase-inhibitors-and-dmards-in-patients-with-active-rheumatoid-arthritis-a-bayesian-network-meta-analysis/.
- Schneider B, Peacock E. Understanding the Rheumatologist-Patient Relationship in Treating Rheumatoid Arthritis [abstract]. Arthritis Rheumatol. 2020; 72 (suppl 10). https://acrabstracts.org/abstract/understanding-the-rheumatologist-patient-relationship-in-treating-rheumatoid-arthritis/.
- Curtis J, Emery P, Karis E, Haraoui B, Bykerk V, Yen P, Kricorian G, Chung J. Maintenance of Remission After Withdrawal of Etanercept or Methotrexate in Patients with Rheumatoid Arthritis in Sustained Remission on Combination Therapy: Results from a Randomized, Double-blind, Controlled Trial [abstract]. Arthritis Rheumatol. 2020; 72 (suppl 10). https://acrabstracts.org/abstract/maintenance-of-remission-after-withdrawal-of-etanercept-or-methotrexate-in-patients-with-rheumatoid-arthritis-in-sustained-remission-on-combination-therapy-results-from-a-randomized-double-blind-co/.
- Ard.bmj.com Treating rheumatoid arthritis to target 2014 update of the recommendations of an international task force by Smolen 2016
- wchh.online library.wiley.com Summary of the new EULAR rheumatoid arthritis guidelines by Chaplin 2020
  Ard.bmj.com 20. EULAR definition of difficult to treat rheumatoid arthritis
- www.ncbi.nim.nih.gov JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the
  Emerging Clinical Data

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Questions?