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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Rheumatoid Arthritis 2021

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Faculty Disclosure

Wendy Simmons, PA-C:

- Speaker: Abbvie, Amgen, BI, Radius, Pfizer, UCB, Celgene
- Advisory Board: Abbvie, Amgen, Celgene, Janssen
- Consultant: Abbvie, Amgen, Celgene

Danielle Gatti-Palumbo, Pharm.D., BCACP:

- There are no financial relationships to disclose

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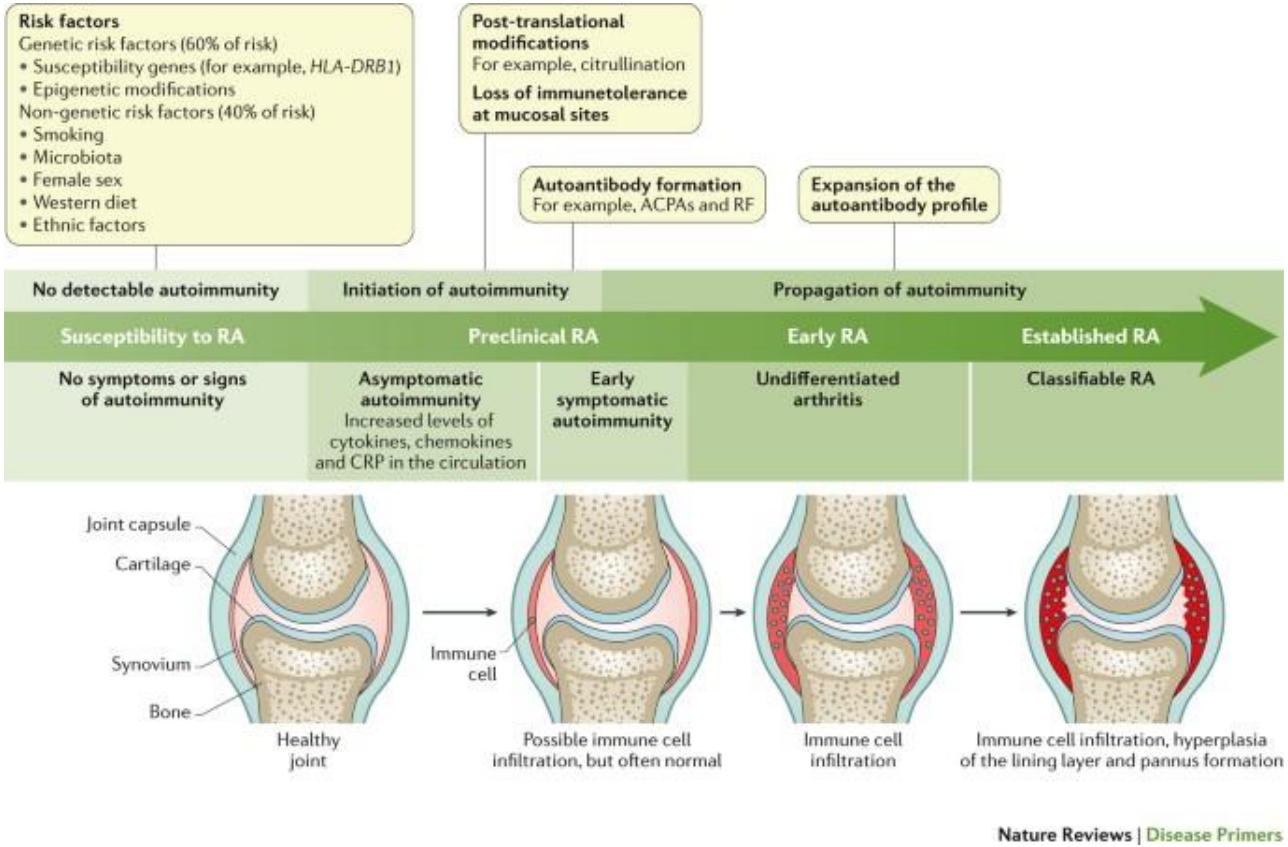
Rheumatoid Arthritis 2021 Susceptibility to Established RA With EULAR 2021 Reviews

Wendy Simmons, PA-C, DFAAPA
Carolina Arthritis Associates

Objectives

- Brief review Genetics/Environmental Triggers of preclinical RA
- Effects of smoking with + CCP antibody
- EULAR review, second hand smoking effects
- Case study following patient from susceptibility to established RA
- EULAR review OPAL study switching JAK’s

4 Stages of RA



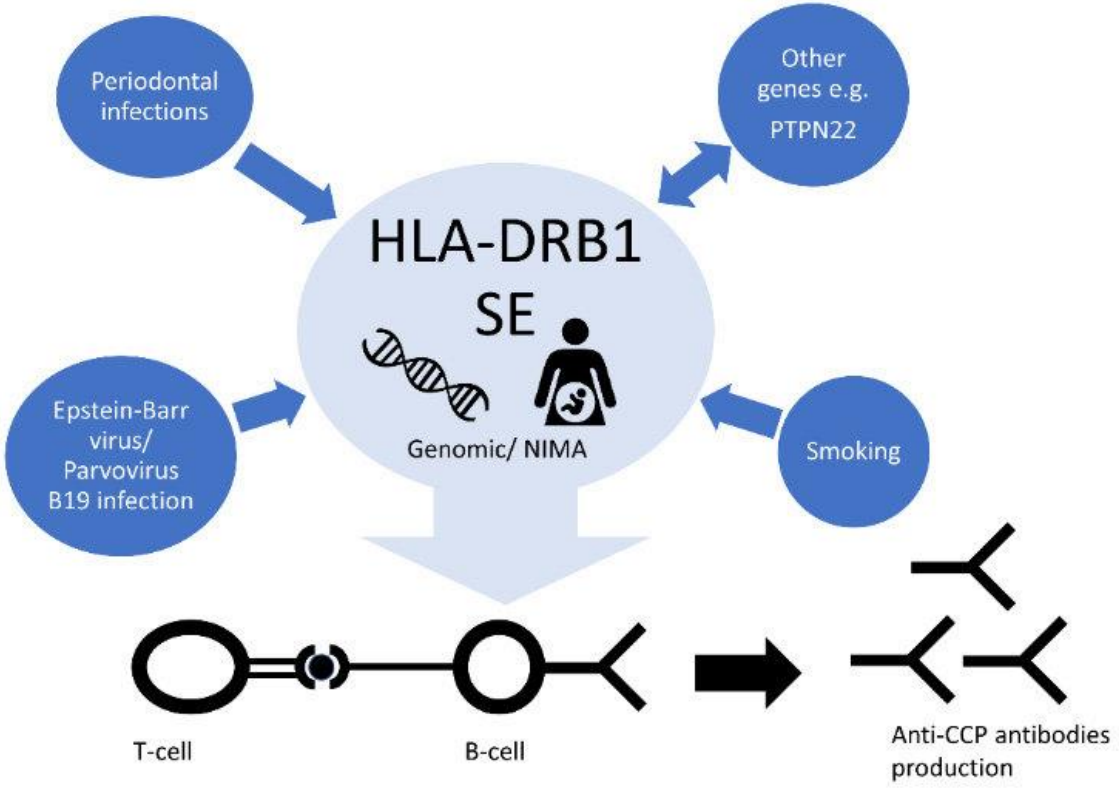
Family History and Genetics

- Over 100 genetic changes occurring more commonly in patients with RA.
- Years of studies confirming relatives of individuals with RA had increased risk of getting RA compared to general population.
- First degree relatives of patients with RA were 3 x more likely to develop RA.
- Disease rate in FDR of RA patients is only 0.8% compared to 0.5% in general population showing genes only slightly increase the risk for RA and environmental triggers have a stronger role.

Twin Studies

- Studies provide evidence genes contribute to risk of RA.
- Identical twins (sharing 100% of their genes), more likely to both have RA than non-identical twins (sharing 50% of their genes).
- Study in UK showed both twins had RA in 15% of sets of ID twins compared to 4% of non-ID twins.

HLA-DRB1 Interactions



Genetics

- Tell my patients in clinic, usually a genetic predisposition with environmental triggers.
- Evaluate to determine if patient has RA and if so where is that patient on spectrum.
- HLA-DRB1 is the major genetic susceptibility locus for RA pathogenesis.
- RA shared epitope, 5 amino acid sequence on HLA-DRB chains encoded by HLA-DRB1 alleles strongly associated with susceptibility to severe RA.

Genetics

- RA shared epitope acts as a ligand that interacts with cell surface calreticulin activating immune dysregulation.
- Citrullinated calreticulin is overabundant in RA synovium.
- Proteins produced from HLA genes help immune system distinguish body’s own proteins from proteins made from foreign invader (virus/bacteria).
- HLA-DRB1 shared epitope alleles do not independently contribute to progression of RA but contribute to development of anti-CCP antibodies.

Environmental Triggers

Periodontal bacteria

- Aggregatibacter actinomycetemcomitans (Aa) triggers hypercitrullination in human WBC's, the major source of citrullinated proteins in RA.
- Aa causes hypercitrullination by secreting toxin called leukotoxin A (LtxA) that makes holes in WBC's as a self defense strategy to kill host immune cells.
- Studies show almost half patients with RA have evidence of Aa infection, compared to 11% healthy individuals.
- Exposure to Aa was an important factor for production of antibodies to citrullinated proteins (ACPA) in patients with genetic susceptibility to RA.

Environmental Triggers

Gut microbiomes

- Prevotella dominant in intestine of patients with preclinical RA.
- Low diversity of gut microbiota and dysbiosis in patients with RA.
- In patients difficult if gut microbiota are cause of disease, autoimmune response precedes onset of clinical symptoms 1-10 years.

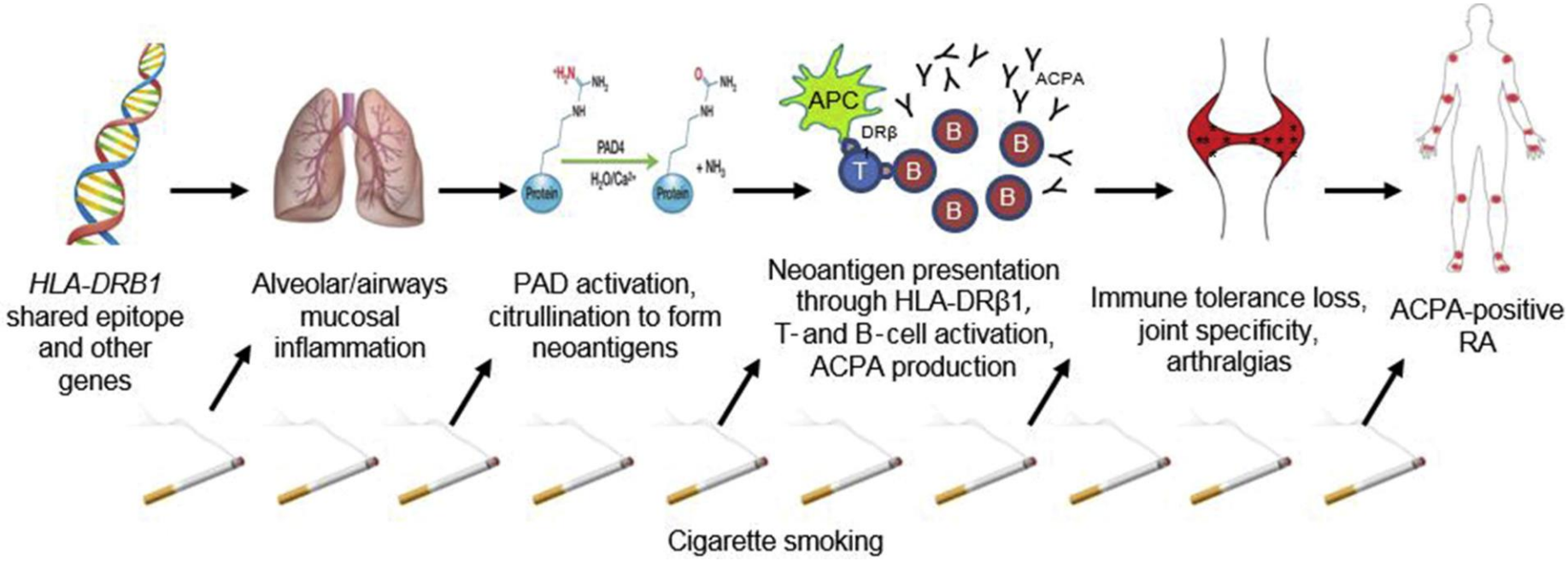
Obesity

Infections

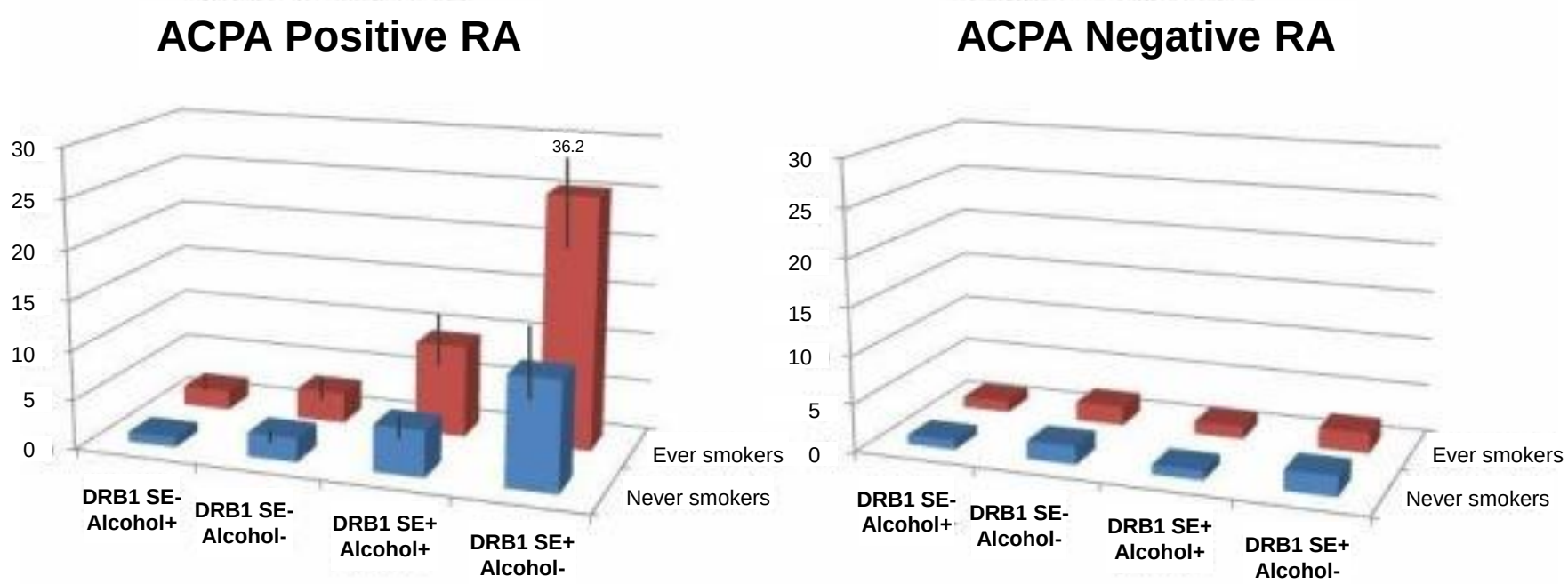
Stress

Tobacco

Cigarette Smoking



Smoking HLA Genes



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Abstract: OP0012 (2021)
ASSOCIATION BETWEEN PASSIVE SMOKING IN CHILDHOOD AND ADULTHOOD, AND RHEUMATOID ARTHRITIS: RESULTS FROM THE FRENCH E3N-EPIC COHORT STUDY

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EULAR OP0012

EULAR OP0012

Background/Objectives

- Rheumatoid arthritis (RA), is a systemic autoimmune disease of multifactorial etiology, which preferentially affects women.
- To date active smoking has been most reproducible reported risk factor for anti-citrullinated protein antibodies (ACPA) positive RA, particularly persons who carry HLA-DRB1-shared epitope (SE) alleles
- Aim to investigate the relationship between passive smoking in childhood (PSc) or in adulthood (Psa), and the risk of incident RA in a large prospective cohort of healthy French women.

EULAR OP0012

EULAR OP0012

Methods/Results

- French prospective cohort study investigating environmental factors associated with chronic diseases, following 98,995 women since 1990.
- Identified women with history of PSc (several hours/day), PSa (1 or more hour/day).
- 79,806 women in study, RA patients (698).
- In whole population PSc was associated with the risk of RA among never smoking women, and not among ever-smoking women.
- In whole population PSa was positively associated with the risk of RA among never smoking women, and not among ever-smoking women.

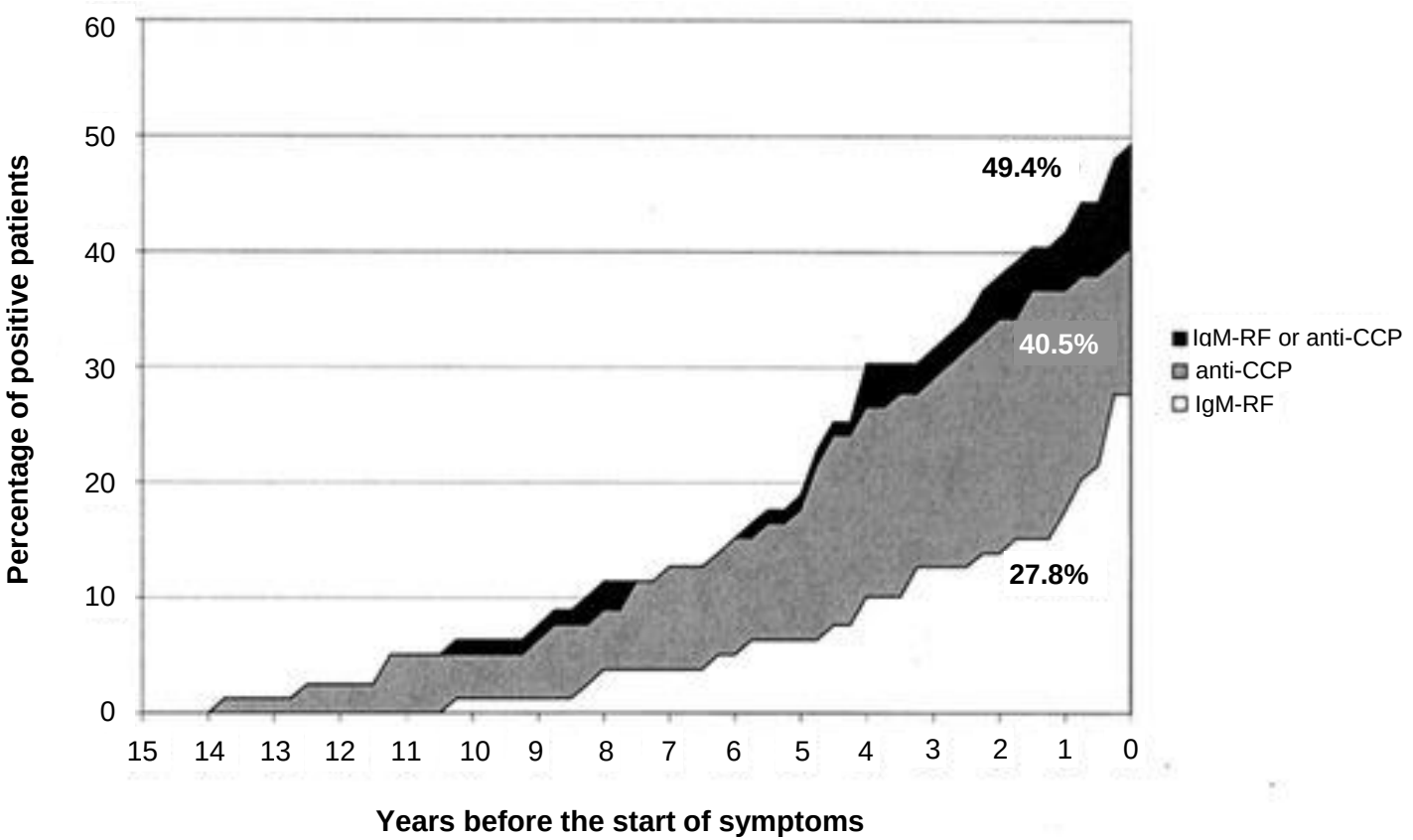
EULAR OP0012

EULAR OP0012

Conclusion

- Passive exposure to smoking in childhood or adulthood increased the risk of RA.
- Association was principally observed among never smoking women.
- Results suggest smoking by-products, whether actively or passively inhaled absorbed, could generate autoimmunity, at least towards antigens involved in RA pathogenesis.

Anti CCP Positivity Prior to Symptoms



Anti-CCP Antibodies

Sensitivity 68% for RA

Specificity 98% for RA

Can be see in active TB, other CTD

Clinical implications

- Predictive of more aggressive disease with more progressive join damage

Dr. Kevin Deane MD/PhD
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Early RA Case Study

History

- 52-year-old petite white female presents 4/2019 for evaluation for symmetrical inflammatory arthritis. Patient is very active, runs half marathons, paddle boarding. Baseline osteoarthritis, history of left great toe fusion with podiatry. Hashimoto thyroid disease, stable, celiac disease, stable.
- 7/2018, developed acute onset of left foot pain and stiffness, evaluated by orthopedics, prescribed heat, NSAID and boot. Discontinued running. Progressive pain, stiffness in feet, (swelling feet), hands, knees, right elbow, morning stiffness lasting 45 minutes- 1 hour, worse in am, better with activity, gelling.
- Denies tobacco, alcohol, or family history of inflammatory arthritis.

Early RA Case Study

Physical Exam

- Right elbow tender, slight 9 degree flexion deformity, normal hands, feet bilateral bunions, MTH's tender, no synovitis detected.
- 4/2019, prescribed Mobic 7.5 mg po qd, while completing evaluation.

Laboratory Studies

- 4/2019, Hct 34.7/Hgb 11.6, normal CMP, ESR 16, CRP 17.9 (4.9), positive RFIgA and RFIgM, negative RFIgA, positive anti-CCP 6.500, negative Hep B/C panel, negative QuantiFeron Gold, uric acid 3.7.

Early RA Case Study

Imaging

- X rays bilateral hands normal, right elbow normal, knees mild patellofemoral degenerative changes, feet, previous left great toe fusion with anchored pin, mild mid foot joint space narrowing, otherwise normal, clear CXR.

Diagnosis

- 5/20/2019, seropositive RA, “hesitant” to proceed with DMARDs, agreed and started Plaquenil 200 mg po bid, continued Mobic 7.5 mg po qd.

Early RA Case Study

Follow Up Visits:

- 2 months: in tears, uncontrolled symptoms, hand and wrist synovitis. Discontinued Plaquenil started Methotrexate 15 mg po q week, folic acid supplements.
- Remained stable, normal labs for 3 month visits until 5/28/2020 (one year).
- Patient called into practice with acute onset of right elbow, pain, swelling, flexion deformity thought to be secondary to “staying inside and doing increased plank exercises”. Brought into office, without signs of trauma or infections, labs normal CBC with diff, ESR 25, CRP 59.

Early RA Case Study

Follow up visit (continued)

- MRI, right elbow, severe synovitis throughout elbow raising concern for inflammatory polyarthropathy such as RA. Reactive bone marrow edema without fracture. Moderate superimposed osteoarthropathy at the trochlear joint.
- Increased Methotrexate 20 mg po q week, prednisone.
- Patient underwent right elbow tensoynovectomy 7/2020.
- Continued MTX 20 mg po q week, added TNF therapy.
- 3 Month follow up stable with TNF.
- 6 month follow up progressive breakthrough stiffness, discontinued TNF.
- JAKi added to MTX.

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EULAR Abstract POS0223
PATTERNS OF JANUS KINASE INHIBITOR CYCLING FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS IN REAL-WORLD CLINICAL PRACTICE: AN ANALYSIS OF THE OPAL DATASET

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Background/Objectives

Abstract POS0223

- Currently 11 biologic and targeted synthetic (b/tsDMARDs) for treatment of RA in Australia
- Cost of b/tsDMARDs subsidized by government for patients with active RA despite 6 months of csDMARD therapy
- October 2015, first JAK approved (tofacitinib,TOF), September 2018 baricitinib (BARI), and May 2020 upadacitinib (UPA)
- Each of these oral tsDMARDs possess different selectivity profiles towards different members of the JAK family (JAK 1-3 and Tyk 2)
- **Aim of analysis to determine the patterns of JAK cycling in real-world practice in Australia**

Methods

Abstract POS0223

- Clinical data sourced from OPAL dataset, collected from EHR during routine consultation.
- Patients > 18 with RA treated with b/tsDMARD Jan 2007-Dec 2020.
- Data included medication initiation/cessation dates, reason for stopping tsDMARD recorded in medical record at time of decision.

Results

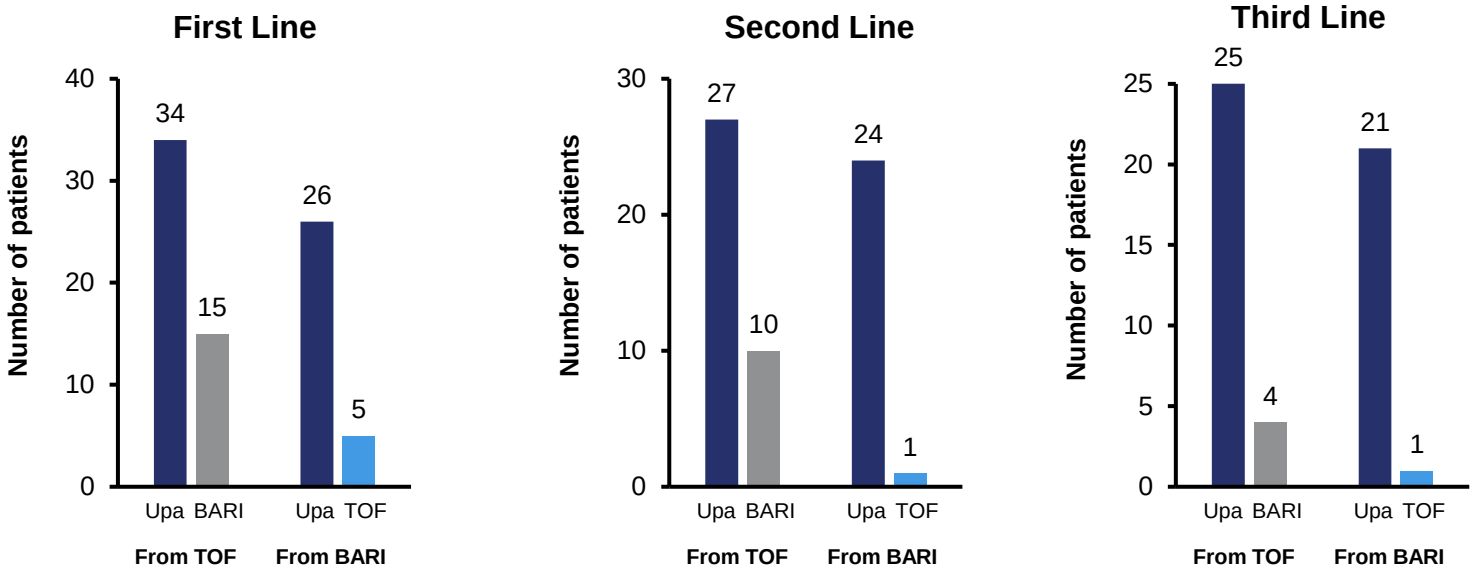
Abstract POS0223

- At December 2020, 52,190 patients with RA in the OPAL dataset, 28% prescribed b/tsDMARDs.
- 3,850 (26.3%) prescribed JAKi-TOF (51.4%), BARI (29.2%), UPA (19.4%)
- In 2020, JAKi initiations (48.8%) of all initiations, (30.7%) of 1st line initiations, increased by 6.1% and 3.5% since 2019, respectively.
- Switch from 1st line JAKi to 2nd line JAKi, 33.1% (2019) to 42.6% (2020)
- Cited lack of efficacy for discontinuation 26.2% (2019, 45.8% (2020)

Patterns of JAKi Cycling for the Management of Rheumatoid Arthritis in First, Second and Third Line Switching

May 2020 – December 2020 with 3rd JAKi (UPA), 1st, 2nd and 3rd line switching (Fig 1.)

Figure 1.



S. Ciciriello et al. *Ann Rheum Dis*. 2021;80:330-331.

ARD

Conclusions

- Significant and sustained uptake of JAKi for management of RA in Australia and JAKi cycling is increasingly common in routine clinical care.
- Clinical outcomes and persistence following JAKi cycling requires further investigation.

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Nras.org.uk The genetics of rheumatoid arthritis (RA) NRAS

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Drug Therapy in RA

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Objective

- Review medications in RA
- Evaluate the current guideline drug recommendations

Classes of Medications

- Conventional DMARDS (csDMARDs):
  - hydroxychloroquine (HCQ), sulfasalazine (SSA), methotrexate (MTX), leflunomide (LEF)
- Biologic DMARDs (bDMARDs):
  - TNF-α inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol)
  - T cell costimulatory inhibitor (abatacept)
  - IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)
- Targeted Synthetic DMARDs (tsDMARDs):
  - JAK inhibitors (tofacitinib, baricitinib, upadacitinib)

Conventional DMARDs

	MTX	LEF	SSZ	HCQ
Dose	10 to 15 mg once weekly, increased by 5 mg every 2 to 4 weeks to a maximum of 20 to 30 mg once weekly SQ: initial 7.5mg, then titrate	20 mg once daily Can give loading dose: 100mg daily x 3 days Can reduce to 10mg daily for tolerability	500mg twice a day Maintenance dose: 2 g/day in 2 divided doses Max: 3g/day	200 to 400 mg/day as single dose or in 2 divided doses Limit retinal toxicity, max daily dose 5mg/kg/day or 400mg, whichever lower
ADR	N/D- Can switch to SQ Mouth sores Alopecia Anemia Myelosuppression Birth defects/pregnancy NO ALCOHOL Hepatotoxicty GI toxicity Tumor lysis syndrome	N/D/HA Rash Alopecia Peripheral neuropathy Abdominal pain Myelosuppression Birth defects/pregnancy NO ALCOHOL Hepatotoxicty	N/V/D/HA Rash Heart burn/ GI distress Oligospermia Orange/yellow skin and urine Photosensitivity- counsel on SPF USE!	N/D/HA Vision changes Rash Worsening psoriasis Joint pain Fatigue
Monitoring	CBC SCR LFT- every 4-8 weeks Infection	CBC SCR LFT- every month x 6 months, then every 4-8 weeks Infection	CBC every 2-4 weeks x 3 months, then every 3 months LFT GI distress Safe in pregnancy	SCR Eye exam every 12 months Visual changes

Tumor Necrosis Factor α (TNF-α)

- RA shows combined TNF-α and interleukin-6 dependency
- **TNF-α**
  - First key cytokine targeted and proved effective in RA
  - Product of neutrophils and activated T cells found in inflamed synovial membrane and entheseal structures in arthritis and in intestinal wall in IBD
  - TNF-α inhibition effective in all major forms of arthritis (RA, PSA, and axial SpA)
  - Etanercept, a dimeric fusion protein, mainly targets soluble TNF-α and is effective in arthritis rather than in IBD
  - Infliximab, adalimumab, certolizumab, and golimumab, antibodies that block soluble and membrane-bound TNF-α are effective in both RA and IBD
  - Specific signaling pathways differ among disease entities

Biologic DMARDS: Anti-TNF

First Line if Incomplete Response or Can Not Tolerate DMARD

	Adalimumab	Infliximab	Etanercept	Golimumab	Certolizumab
Availability	SQ (pens, syringes) CF (citrate-free) 40mg/0.4ml	IV	SQ (pens, syringes, vials, mini device)	IV/SQ	SQ (syringe, vials)
	Adalimumab-atto Adalimumab-adbm, Adalimumab-adaz Adalimumab-afzb (2023) Adalimumab-bwwd Adalimumab-fkjp (7/23)	Infliximab-dyyb Infliximab-axxq Infliximab-abda	Etanercept-szzs Etanercept-ykro		
Dosing	40mg SQ every 2 weeks May increase to 40mg weekly or 80mg every 2 weeks if not responding or not on MTX	3mg/kg/dose IV on week 0,2,6, followed by maintenance dose of 3mg/kg every 8 weeks Can do 10mg/kg every 8 weeks or increase frequency to every 4 weeks if incomplete response Use with MTX	50mg weekly 25mg twice weekly with or without MTX Latex free vials Lower risk of infection	IV: 2mg/kg at week 0,4, then every 8 weeks SQ: 50mg monthly With MTX	400mg at week 0,2,4 then 200mg every other week or 400mg monthly Safety data in pregnancy/ breastfeeding Can bill medical
Monitoring: LFTS, TB, Hep-B, Infection, Malignancy, Skin rash-psoriasis, Worsening CHF, +ANA-Lupus like, Pancytopenia					

Biologic DMARDS: Non-TNF

	Rituximab	Abatacept
Mechanism	Blocks CD-20 B-cells	Inhibits T-cell Activation
Availability	Rituximab-abbs Rituximab-arrx Rituximab-pvvr	
Dose	IV: 1,000mg on days 1 and 15 Subsequent courses every 24 weeks or sooner every 16 weeks Premeds: methylprednisone 100mg IV 30 min prior With MTX	IV: 60KG: 500mg 60-100KG: 750mg >100KG: 1,000mg At week 0,2, 4, then every 4 SQ: 125mg weekly Loading dose if needed: IV Dose x1, then 125mg SQ within 24 hrs
Monitoring	GI Perforation, Cardiovascular, lymphopenia, leukopenia, neutropenia, thrombocytopenia, and anemia, CBC, Hep B, TB, Infusion reactions, Infections, Mucocutaneous reactions, Progressive multifocal leukoencephalopathy (PML), Tumor lysis syndrome, SCR	Infection, hypersensitivity reactions, Malignancy, COPD

Interleukin-6 (IL-6)

- Inhibition (tocilizumab and sarilumab), effective in RA, not in axial SpA and PSA
- Use in RA initially based on inhibiting T-cell– mediated B-cell activation, which is important for the generation of autoantibodies
  - IL-6 inhibition does not significantly lower autoantibody levels in RA
- Single-cell sequencing studies of synovial tissue in RA show IL-6 as a major product of resident synovial fibroblasts, combined with chemokines bring immune cells into joint
- IL-6 receptor inhibition has higher therapeutic specificity for RA than TNF-α inhibition, not higher therapeutic efficacy
- IL-6 receptor inhibitors and Janus kinase (JAK) inhibitors
  - IL-6 and JAK inhibitors correct suppressed bone formation in RA and induces partial repair of damaged joints
  - JAK inhibitors partially act by inhibiting IL-6 receptor signaling
  - Monotherapy significantly better therapeutic response than MTX in treatment-naive RA

Biologic DMARDS: Non-TNF
Interleukins

IL-1	IL-6
Anakinra SQ – 100mg daily	**Tocilizumab** IV: 4mg/kg every 4 weeks, may increase to 8mg/kg every 4 weeks (max 800mg) SQ <100kg: 162mg every other week, may increase to weekly >100kg: 162mg weekly IV to SQ: Give SQ dose at time of next scheduled dose **Sarilumab** SQ- 200mg every 2 weeks
	Not recommended with diverticulitis/ GI Perforation With or without DMARDs Do not initiate if ANC <2,000/mm3, PLTs <150,000/mm3, AST/ALT >1.5x ULN
Monitoring: CBC, Neutropenia, Leukopenia, Thrombocytopenia, LFTs, Hyperlipidemia, Infection, TB, Malignancy	

Target Synthetic DMARDS
Janus Kinase (JAK) Inhibitors

Tofacitinib	Baracitinib	Upadacitinib
Jak 1,2,3	Jak 1,2	Jak 1
IR: 5mg twice daily XR: 11mg once a day	2mg daily	15mg daily
IR: 5mg once a day XR: Transition to 5mg IR	EGFR 30-60ml/min: 1mg daily EGFR <30ml/min: Not recommended	EGFR <15ml/min not studied

With/without DMARDs

Do not initiate with absolute lymphocyte <500cells/mm3, ANC<1,000cells/mm3, Hgb<8g/dl

Monitoring: CBC, SCR-renal dose, Lymphocytopenia, Neutropenia, Anemia, GI perforation, LFT, Hep B, Infections, TB, **Lipid abnormalities**, **Malignancy**, Interstitial lung disease (ILD), **Thrombosis, Herpes Zoster**

Increased risk of death in RA patients age >50 + 1 **cardiovascular** risk factor

2021 ACR Guidelines

Clinical scenario	2021 ACR guideline[2]	2019 EULAR recommendations[3]
First-line therapy	Low disease activity: hydroxychloroquine	Methotrexate (in absence of contraindications)
	Moderate-to-high disease activity: methotrexate	
Use of glucocorticoids	Conditional recommendation against glucocorticoids when starting csDMARDs	Consider short-term glucocorticoids when starting or switching csDMARDs
Insufficient response to methotrexate	Add bDMARDs or tsDMARDs	Poor prognostic factors absent: consider other csDMARDs
		Poor prognostic factors present: add bDMARDs or tsDMARDs
Drug tapering in persistent remission	Continue all DMARDs	Taper glucocorticoids first, then consider tapering bDMARDs or tsDMARDs, then csDMARDs
	If tapering is considered, taper methotrexate, not bDMARDs or tsDMARDs	

bDMARDs, biologic DMARDs; csDMARDS, conventional synthetic DMARDs; RA, rheumatoid arthritis; tsDMARDs, targeted synthetic DMARDs.

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Special Populations

Subcutaneous nodules

- MTX > other DMARDs
- Switching to non-methotrexate DMARD > continuation MTX with progressive nodules

Pulmonary disease

- MTX > other DMARDs

Heart Failure

- Non-TNF inhibitor bDMARD or tsDMARD > TNFi who failed csDMARDs or who developed HF while on anti-TNF

Lymphoproliferative disorder

- RTX > other DMARDs

Hepatitis B Infection

Starting with	HBcAb	HBsAg	Recommendation
RTX	+	+/-	Prophylactic antiviral therapy > monitoring alone
bDMARD or tsDMARD	+	+	
bDMARD other than RTX or a tsDMARD	+	-	Frequent monitoring alone > prophylactic antiviral therapy

Special Populations

Nonalcoholic fatty liver disease

- MTX > alternative DMARDs for DMARD-naive patients, normal LFTs, and no evidence of advanced liver fibrosis

Persistent hypogammaglobulinemia, no infection

- Continue RTX in pts at target > switching to different bDMARD or tsDMARD

Previous serious infection

- csDMARDs > addition of a bDMARD or tsDMARD for pts who failed csDMARDS monotherapy
- Addition of/switching to DMARDs > initiation/ dose escalation of GC

Nontuberculous mycobacterial lung disease moderate-to-high disease activity despite csDMARDs

- Lowest possible dose of GC (d/c if possible) > continuation of GC
- csDMARDs > addition of a bDMARD or tsDMARD
- Abatacept > other bDMARDs and tsDMARDs

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