Lessons From Rheumatology- How To Make Rationale Decisions In A Multi-drug Era

Dr Frances Humby MRCP PhD
Senior Lecturer and Honorary Consultant Rheumatologist
Centre for Experimental Medicine and Rheumatology
William Harvey Research Institute
Queen Mary University of London

Ferring Pharmaceuticals have reviewed these slides for technical content

PA/2250/2019/UK September 2019

Disclosures

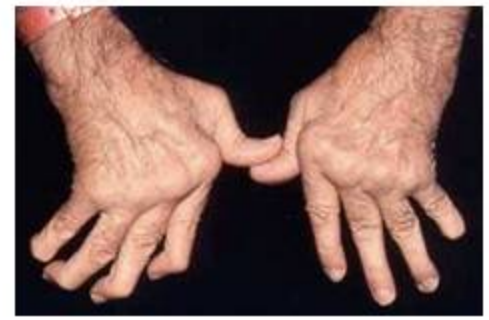
- Received fees/honorarium/consultancy fees from Pfizer, Roche, Abbvie and BMS.

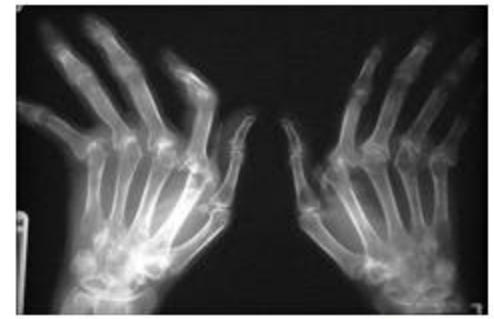
Outline

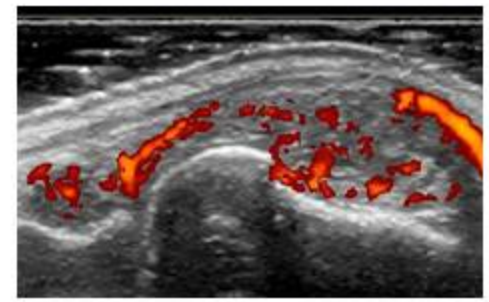
- Journey to advanced therapies in RA
- How we select therapies for RA patients
- Unmet need
- Clinical cases - MCQs

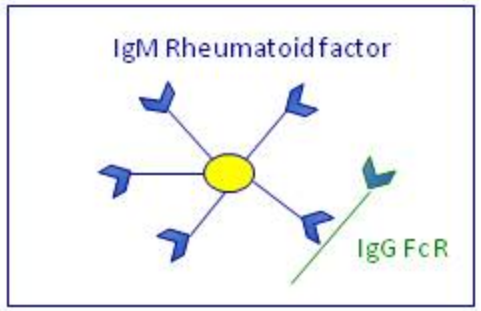
Rheumatoid arthritis

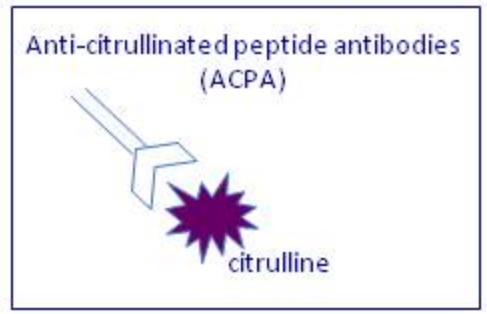
- 1% of UK population
- £8bn direct costs to UK economy



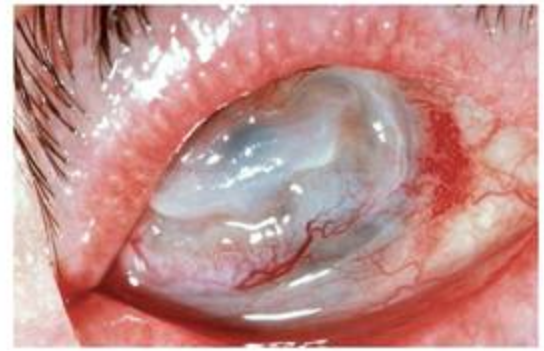


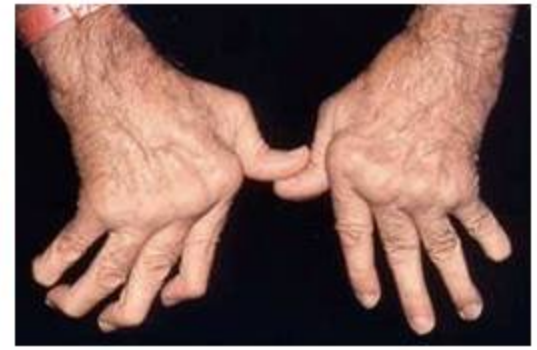


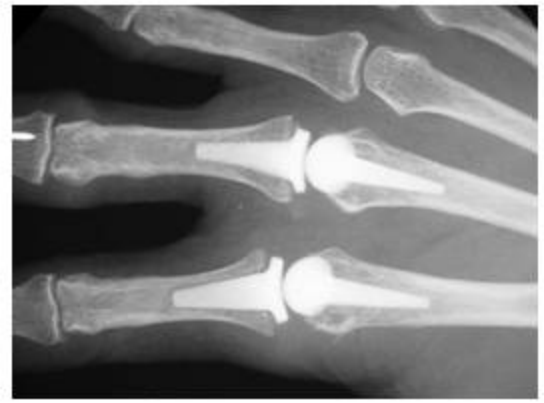


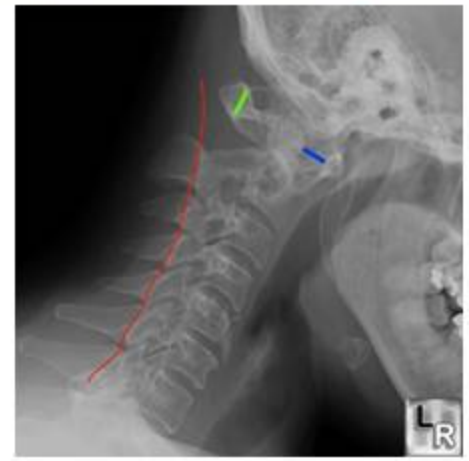


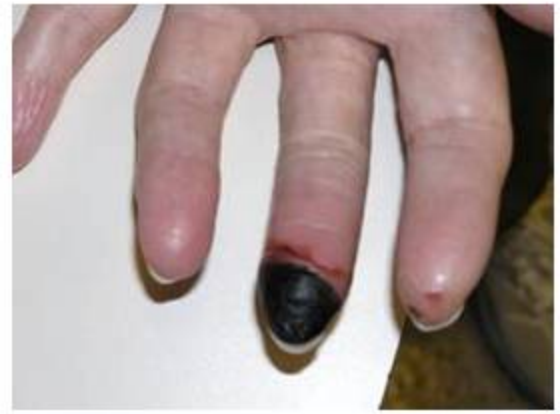

© 2009

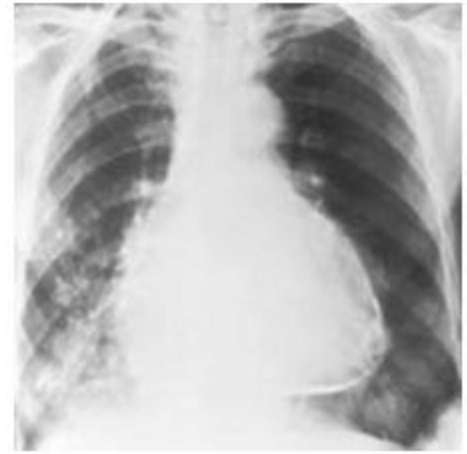




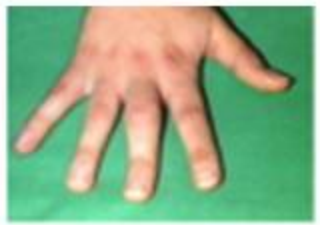


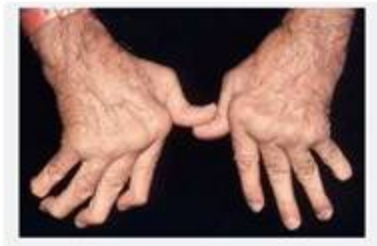






Early window of opportunity in RA





3-6 months

2 years: 90% patients
Radiographic erosions

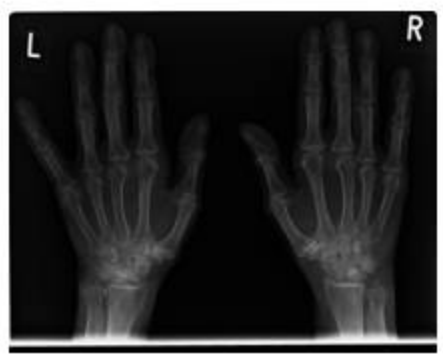
Increased morbidity
and mortality

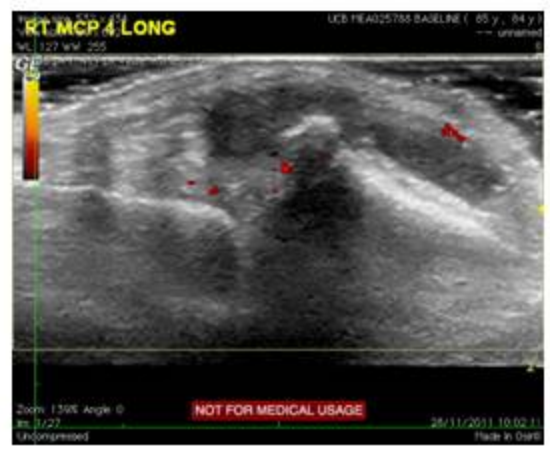
Disease onset

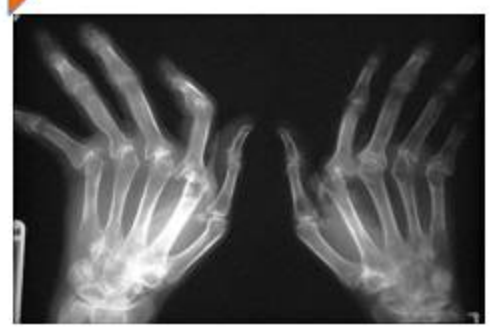
Early

Established

Late Stage







BARTS ARTHRITIS CENTRE
Early Arthritis Clinic

Consultants: Prof C. Pitzalis, Dr S Kelly and Dr F Humby

Mile End Hospital :Friday am clinic (weekly)
University Hospital Newham:Wednesday am clinic (weekly)

1. Rapid and easy access (< 2 weeks)
2. One stop clinic for diagnosis and treatment
3. Offer patients inclusion in research studies
4. Optimisiation of ongoing care through tight control of disease

Referral Criteria

Patients with a history of inflammatory arthritis and one of:

1. ≥1 swollen joint
2. anti-CCP or RF +ve
3. elevated ESR/CRP

Please do not administer steroids before assessment in the Early Arthritis Clinic

Access to this clinic can be gained by either:
Fax: Urgent referral to rheumatology secretaries
Contacting on call rheumatology team
Choose and book (Rheum early synovitis clinic)

Therapeutic options

Disease modifying anti-rheumatic drugs (DMARDs)			
Synthetic DMARDs		Biologic DMARDs	
	ADVANCED THERAPEUTICS		
Conventional synthetic DMARDs (csDMARDs) • methotrexate • leflunomide • sulphasalasine • hydroxychloroquine	Targeted synthetic DMARDs (tsDMARDs)	Biologic Originator (bo)DMARDs	Biosimilar (bs) DMARDs

What first?

painkillers

Steroids

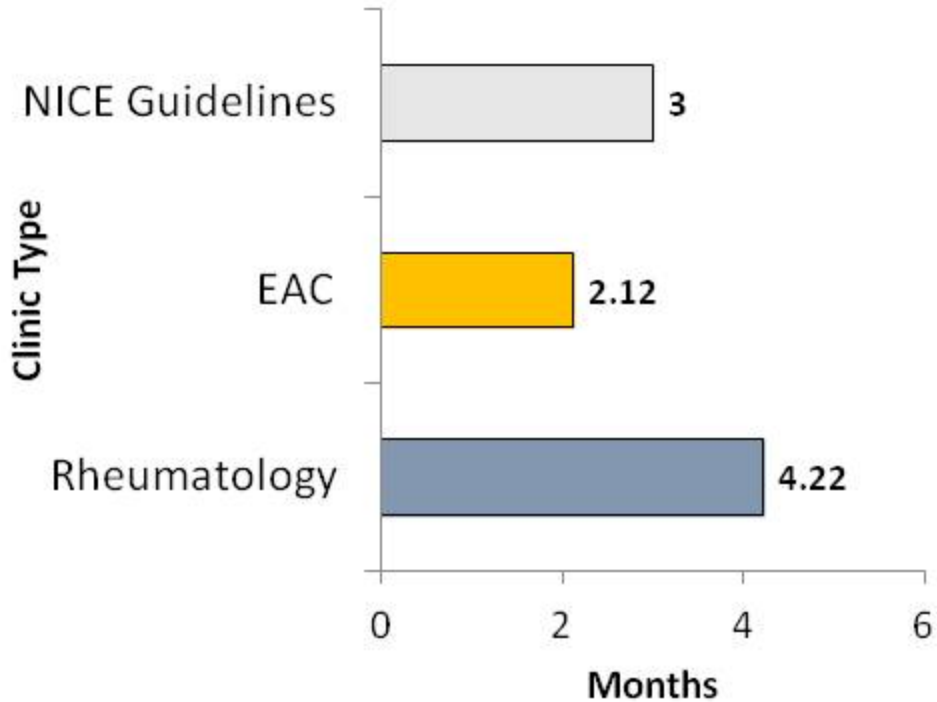
csDMARDs

Advanced therapeutics

NSAIDs

Time to DMARD initiation

Mean time to first DMARD prescription from onset of symptoms/date of diagnosis in EAC compared to Rheumatology clinics.



P=0.0003

Early Arthritis Clinic (n=59)

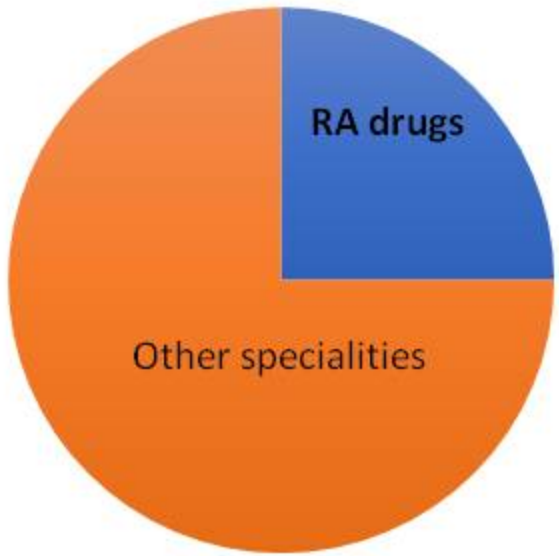
- 89% on DMARDs <3 months
- 66% on DMARDs <2 months
- Range 1-7 months

Rheumatology Clinic (n=69)

- 50% on DMARDs <3 months
- Range 1-18 months

RA drugs count for ¼ specialty spend

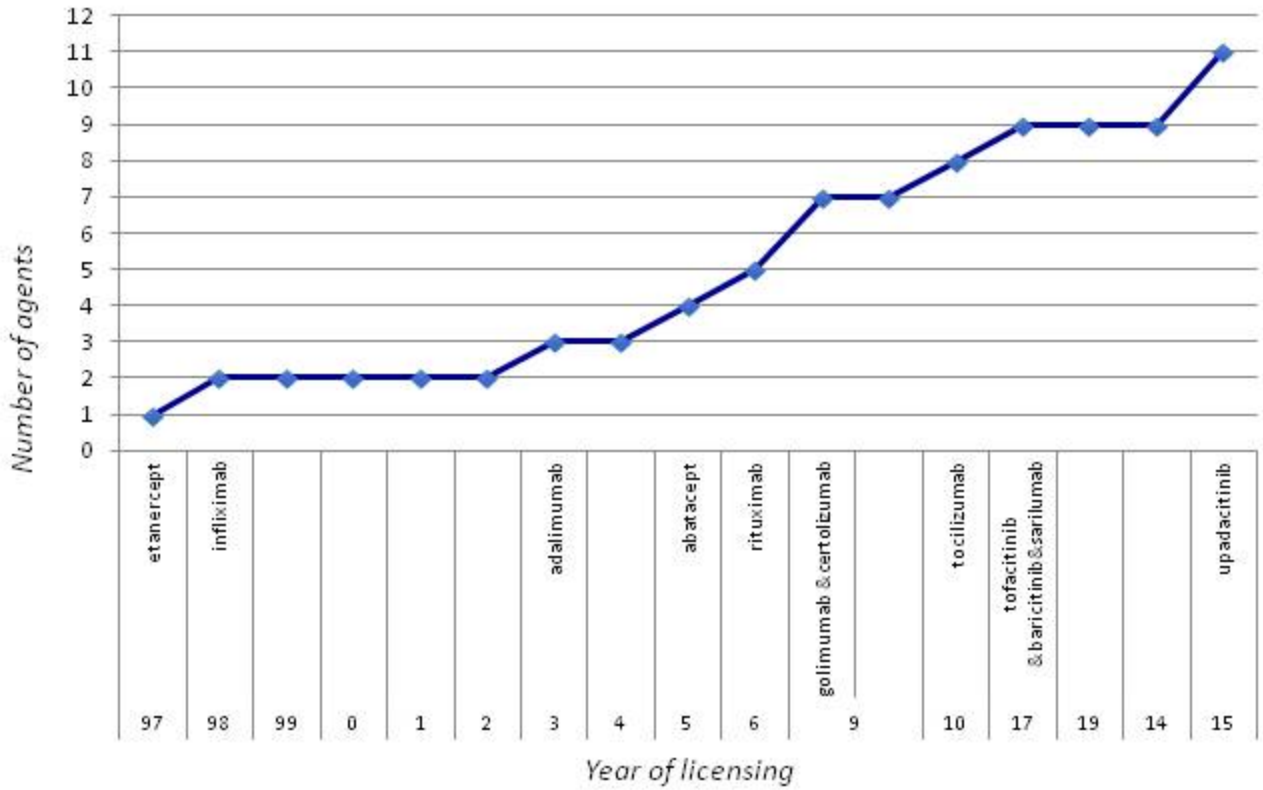
$87 Billion



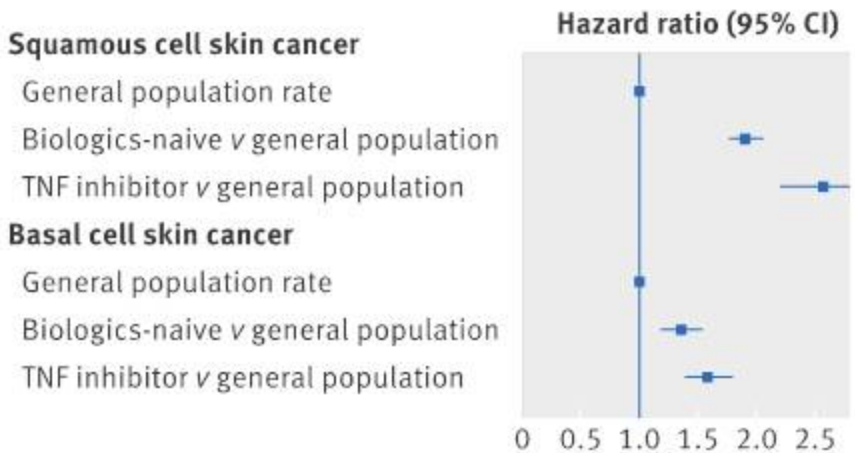
1. Oncology
2. Rheumatology
3. Psychiatry

United Health Centre for Health Reform and Modernisation. Issue Brief. The Growth of Specialty pharmacy: Current trends and future opportunities. April 2014. American Health and Drug Benefits. Trends in Biologic therapies for Rheumatoid arthritis. March April 2012.

Number of advanced therapies for RA patients



Risks of biologic therapy



doi: 10.1136/bmj.i262 | *BMJ* 2016;352:i262

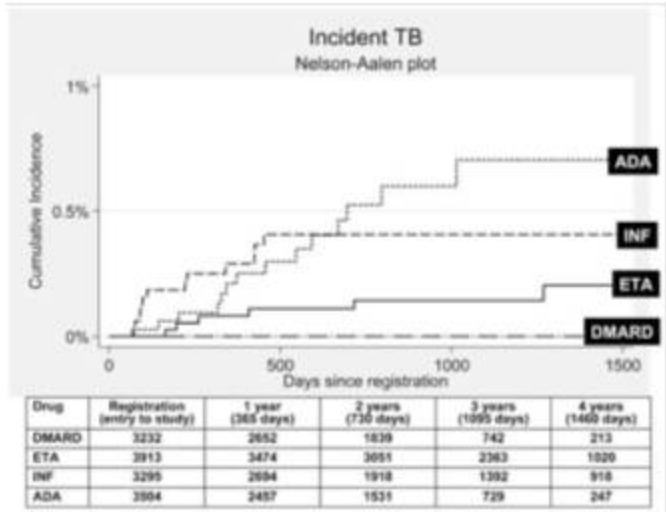


Figure 2 Cumulative incidence of tuberculosis (TB) following first exposure to anti-tumour necrosis factor (anti-TNF) therapy (most recent drug model, with person-years censored at death, last returned follow-up form, or date of switching to second anti-TNF). Numbers in table represent the number of patients eligible for follow-up at the specified follow-up time points. ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; INF, infliximab.

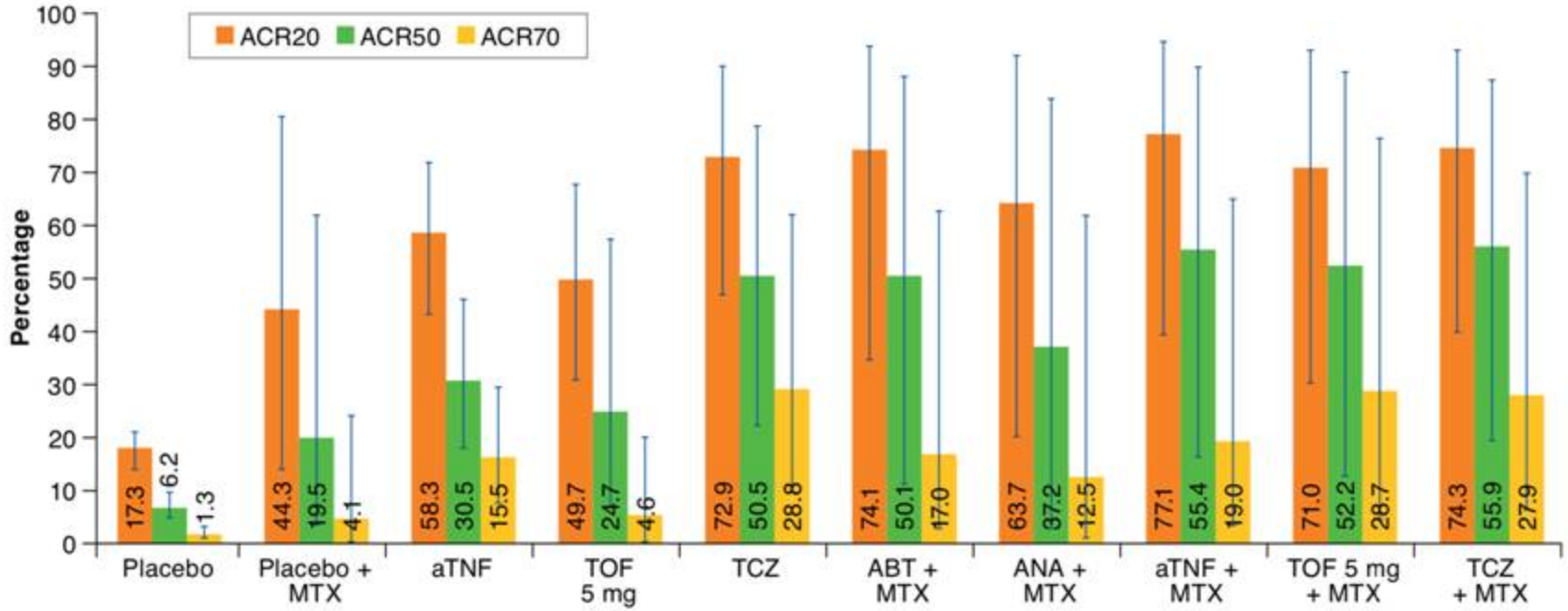
Table 4 Incidence and HR of shingles

Result	nbDMARD n=3673	All TNF n=11 881	Etanercept n=4139	Infliximab n=3475	Adalimumab n=4267
Follow-up (patient-years)	5417	17 048	6122	4529	6397
Shingles events	45	275	99	91	85
Shingles incidence (/100 patient-years)	0.8 (0.6–1.1)	1.6 (1.4–1.8)	1.6 (1.3–2.0)	2.0 (1.6–2.5)	1.3 (1.1–1.6)
Shingles unadjusted HR	Ref	1.9 (1.4–2.6)	1.7 (1.2–2.5)	2.4 (1.7–3.4)	1.7 (1.2–2.5)
Shingles adjusted HR*	Ref	1.7 (1.1–2.7)	1.7 (1.0–2.7)	2.2 (1.4–3.4)	1.5 (0.9–2.4)

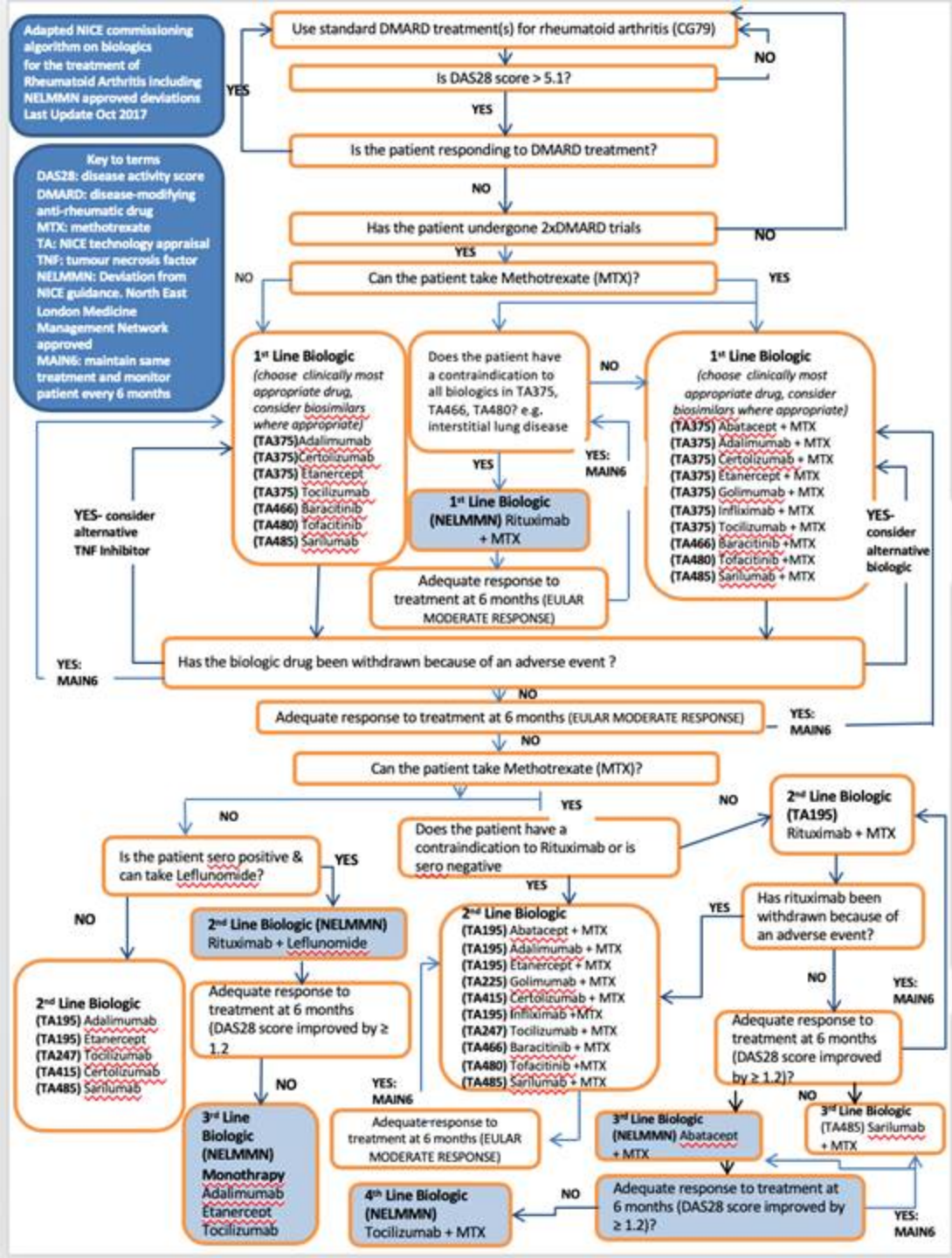
*Adjusted rates using propensity modelling described in the Methods section and using multiple imputations to replace missing baseline variables.
nbDMARD, non-biological disease-modifying antirheumatic drug; TNF, tumour necrosis factor.

Ann Rheum Dis 2013;**72**:229–234. doi:10.1136/annrheumdis-2011-201108

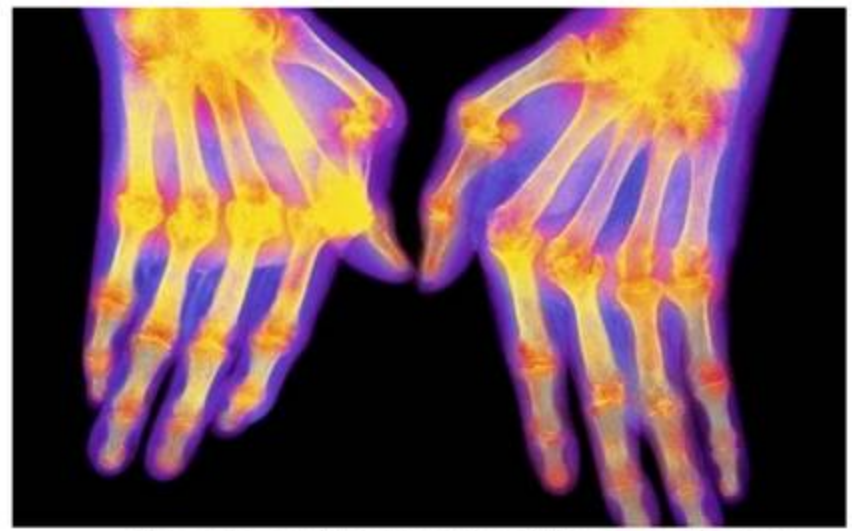
FIGURE 3 Probability of ACR20/50/70 Response with 95% CrI for Different Classes of Biologic Treatment with and Without MTX



ABT = abatacept; ACR20/50/70 = 20%/50%/70% improvement in American College of Rheumatology criteria; ANA = anakinra; aTNF = anti-tumor necrosis factor; CrI = credible interval; mg = milligram; MTX = methotrexate; TCZ = tocilizumab; TOF = tofacitinib.


Adapted NICE commissioning algorithm on biologics for the treatment of Rheumatoid Arthritis including NELMMN approved deviations Last Update Oct 2017
Key to terms
DAS28: disease activity score
DMARD: disease-modifying anti-rheumatic drug
MTX: methotrexate
TA: NICE technology appraisal
TNF: tumour necrosis factor
NELMMN: Deviation from NICE guidance. North East London Medicine Management Network approved
MAIN6: maintain same treatment and monitor patient every 6 months
Use standard DMARD treatment(s) for rheumatoid arthritis (CG79)
NO
Is DAS28 score > 5.1?
YES
YES
Is the patient responding to DMARD treatment?
NO
Has the patient undergone 2xDMARD trials
NO
YES
NO
Can the patient take Methotrexate (MTX)?
YES
1st Line Biologic (choose clinically most appropriate drug, consider biosimilars where appropriate)
(TA375) Adalimumab
(TA375) Certolizumab
(TA375) Etanercept
(TA375) Tocilizumab
(TA466) Baracitinib
(TA480) Tofacitinib
(TA485) Sarilumab
Does the patient have a contraindication to all biologics in TA375, TA466, TA480? e.g. interstitial lung disease
NO
YES: MAIN6
YES
1st Line Biologic (NELMMN) Rituximab + MTX
Adequate response to treatment at 6 months (EULAR MODERATE RESPONSE)
1st Line Biologic (choose clinically most appropriate drug, consider biosimilars where appropriate)
(TA375) Abatacept + MTX
(TA375) Adalimumab + MTX
(TA375) Certolizumab + MTX
(TA375) Etanercept + MTX
(TA375) Golimumab + MTX
(TA375) Infliximab + MTX
(TA375) Tocilizumab + MTX
(TA466) Baracitinib +MTX
(TA480) Tofacitinib +MTX
(TA485) Sarilumab + MTX
YES- consider alternative TNF Inhibitor
YES- consider alternative biologic
Has the biologic drug been withdrawn because of an adverse event ?
YES: MAIN6
NO
Adequate response to treatment at 6 months (EULAR MODERATE RESPONSE)
YES: MAIN6
NO
Can the patient take Methotrexate (MTX)?
NO
YES
Is the patient sero positive & can take Leflunomide?
YES
NO
Does the patient have a contraindication to Rituximab or is sero negative
YES
NO
2nd Line Biologic (TA195) Rituximab + MTX
2nd Line Biologic (NELMMN) Rituximab + Leflunomide
Adequate response to treatment at 6 months (DAS28 score improved by ≥ 1.2
2nd Line Biologic
(TA195) Adalimumab
(TA195) Etanercept
(TA247) Tocilizumab
(TA415) Certolizumab
(TA485) Sarilumab
2nd Line Biologic
(TA195) Abatacept + MTX
(TA195) Adalimumab + MTX
(TA195) Etanercept + MTX
(TA225) Golimumab + MTX
(TA415) Certolizumab + MTX
(TA195) Infliximab +MTX
(TA247) Tocilizumab + MTX
(TA466) Baracitinib + MTX
(TA480) Tofacitinib +MTX
(TA485) Sarilumab + MTX
YES
Has rituximab been withdrawn because of an adverse event?
NO
YES: MAIN6
Adequate response to treatment at 6 months (DAS28 score improved by ≥ 1.2)?
NO
3rd Line Biologic (TA485) Sarilumab + MTX
NO
YES: MAIN6
3rd Line Biologic (NELMMN) Monothrapy
Adalimumab
Etanercept
Tocilizumab
Adequate response to treatment at 6 months (EULAR MODERATE RESPONSE)
3rd Line Biologic (NELMMN) Abatacept + MTX
4th Line Biologic (NELMMN) Tocilizumab + MTX
NO
Adequate response to treatment at 6 months (DAS28 score improved by ≥ 1.2)?
YES: MAIN6

NHS saves record £300 million by switching to cheaper arthritis drug



Adalimumab is given to arthritis patients, and those with inflammatory bowel disease and psoriasis CREDIT: SCIENCE PHOTO LIBRARY

Factors to consider when choosing first line advanced therapy

- Infection risk
- BMI
- Pregnancy/conception
- Interstitial pulmonary disease
- History of TB
- P450 cytochrome inhibitors
- Clot risk
- Malignancy
- SLE overlap
- Risk of GI perforation
- Compliance
- Combination therapy with methotrexate
- Sero positivity

Considering 2nd line or subsequent therapy

- Primary failure to first line or adverse event
- Secondary failure
- comorbidities

Drug levels

Anti-drug antibodies

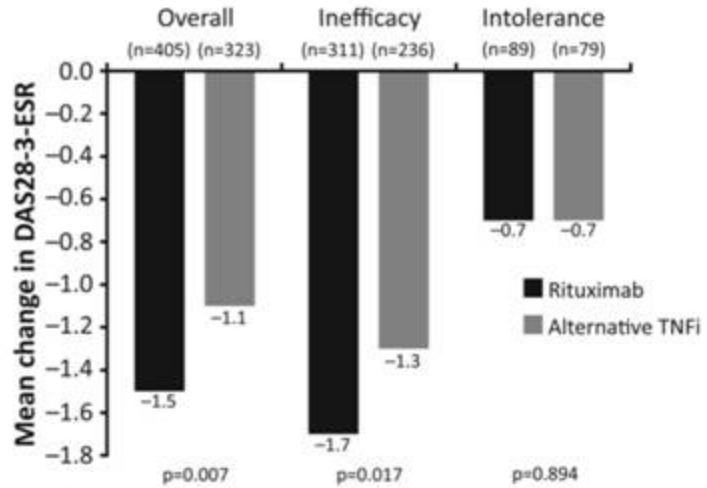


Figure 1 Mean change in Disease Activity Score in 28 joints excluding patient's global health component–erythrocyte sedimentation rate (DAS28-3–ESR) from baseline to 6 months. Analyses were adjusted for baseline value and other covariates found to be statistically significantly different between the two groups at baseline. Values are DAS28-3–ESR least squares means. TFNi, tumour necrosis factor inhibitor.

Emery P, *et al*. *Ann Rheum Dis* 2015;**74**:979–984. doi:10.1136/annrheumdis-2013-203993

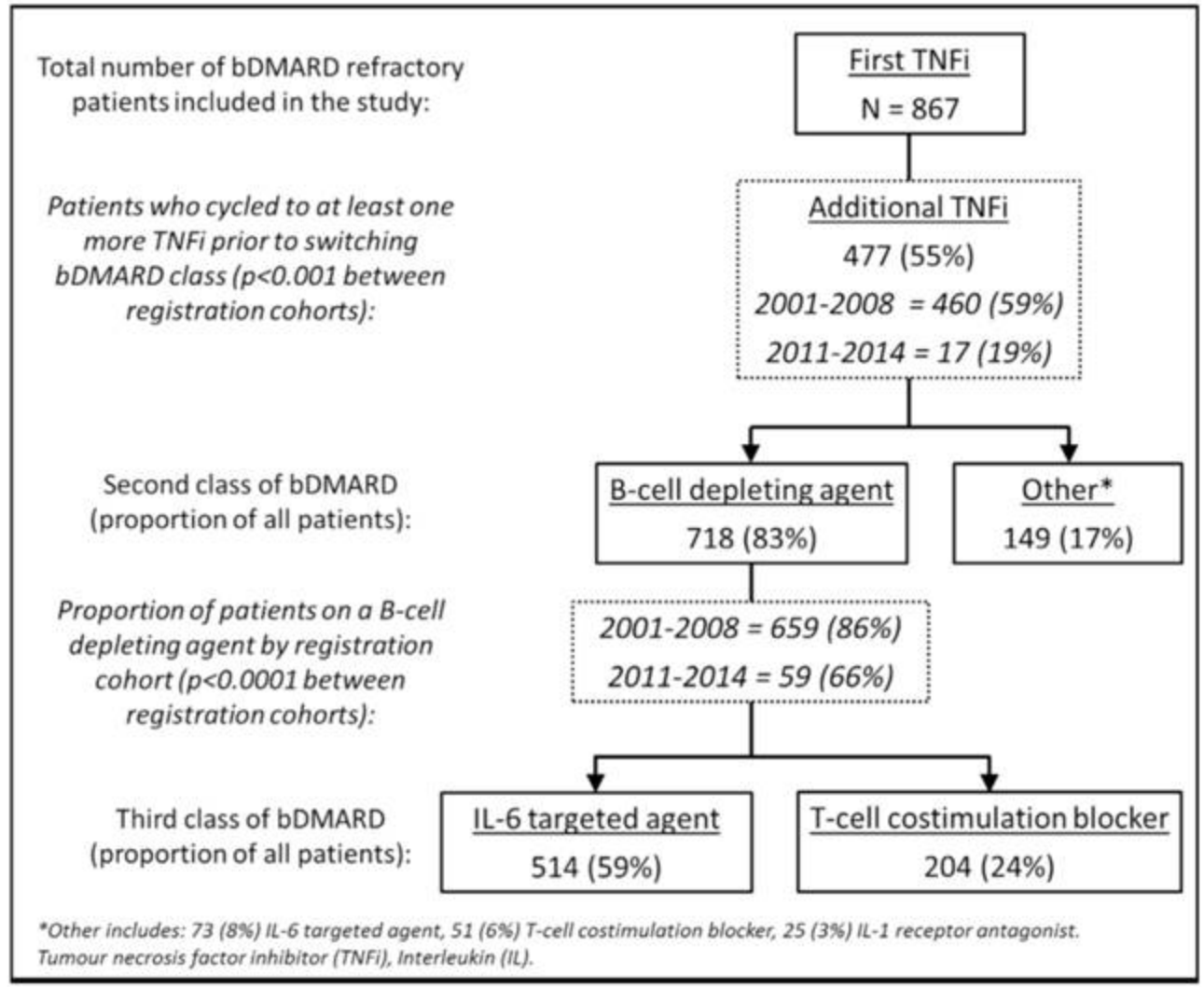
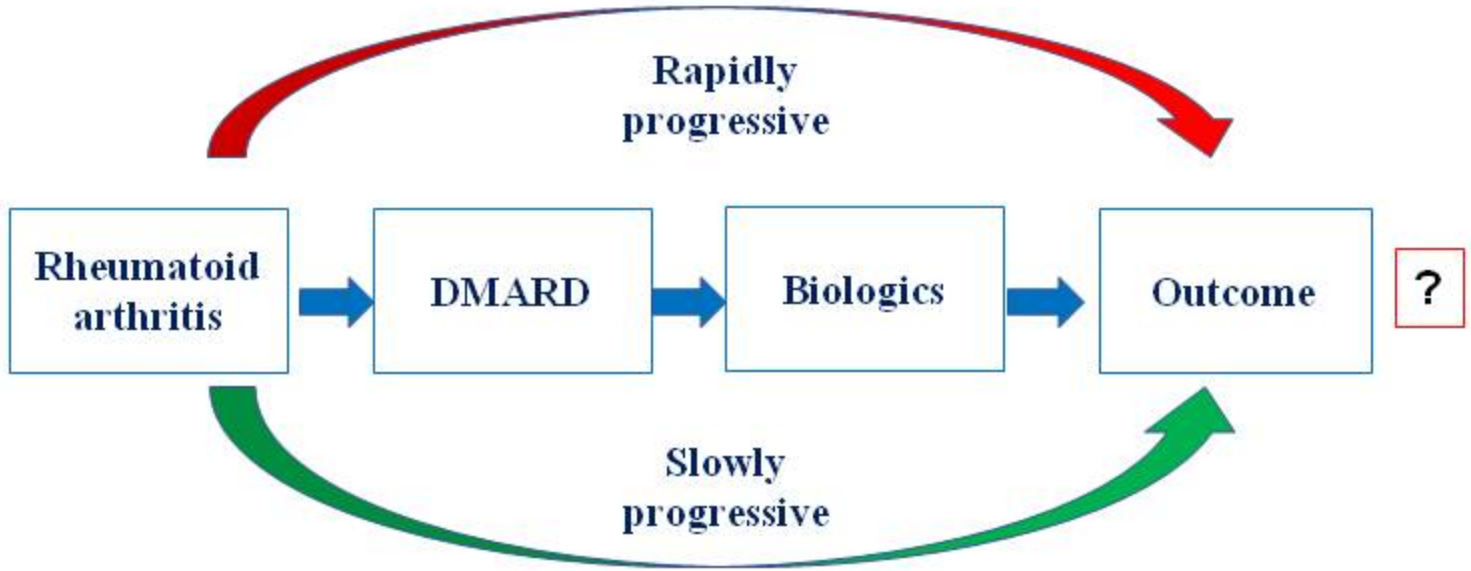


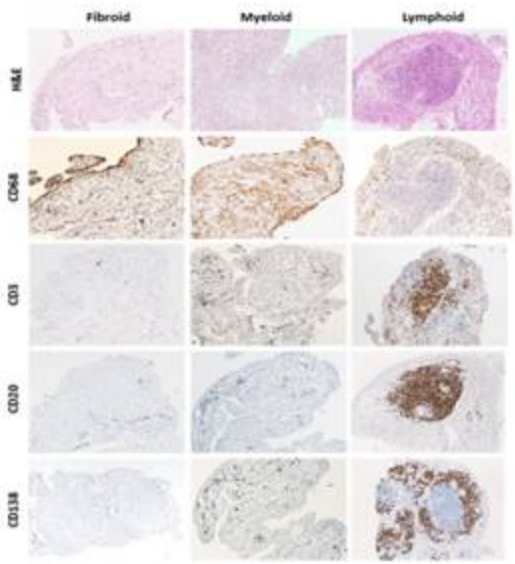
Figure 2 Main pattern of biologic disease-modifying antirheumatic drug (bDMARD) class switching in the 867 bDMARD refractory patients.

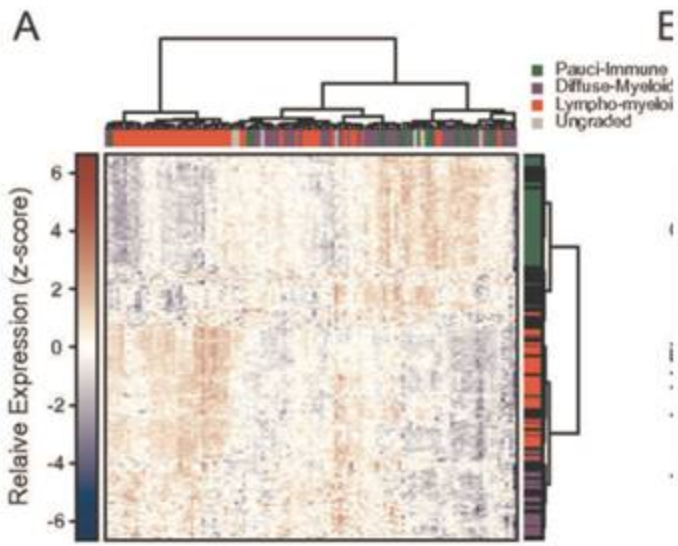
RA is a clinically heterogeneous disease



30-40% of patients will not respond to treatment

RA is clinically and pathobiologically heterogeneous





Does synovial heterogeneity translate to specific

Clinical phenotype

Disease outcome

Response to therapy

Integrated Pathobiology-Driven Patient Stratification Programme

Queen Mary University of London

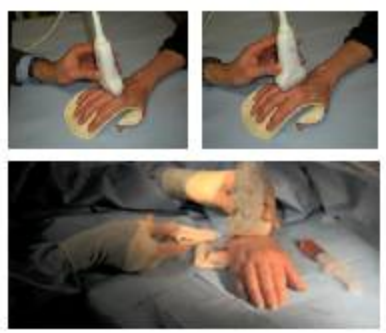
Barts Health NHS Trust

A) MRC-Funded Pathobiology of Early Arthritis Cohort (PEAC)

DMARD Naïve (n=400)

Synovial Bx

DMARD Therapy



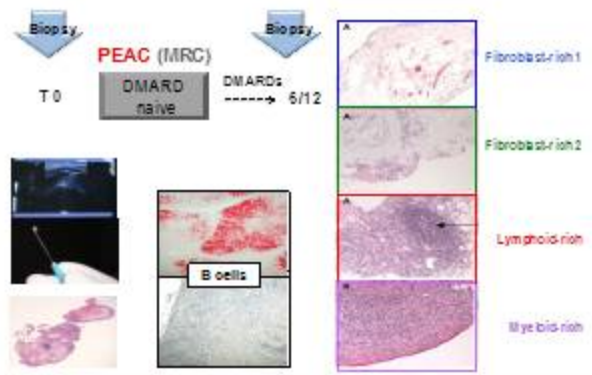
US-guided minimally invasive synovial biopsy

B) MRC/ARUK-Funded MATURA Stratification of Therapy for RA by Pathobiology (STRAP)

DMARD Inadequate Response (n=210)

Synovial Bx

Rituximab | Anti-TNF | Tocilizumab



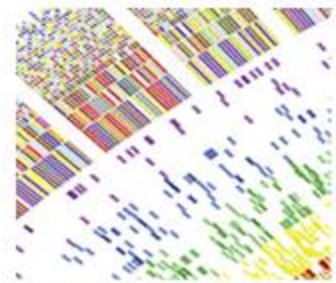
Identification of Tissue Pathotypes (Digital Pathology)

C) NIHR/EME-Funded Mechanisms for Response-Relapse-Resistance to Rituximab in RA (R4-RA)

1st Biologic Failure (Anti-TNF IR) (n=128)

Synovial Bx

Rituximab | Tocilizumab



Identification of Tissue Molecular Pathology Signatures

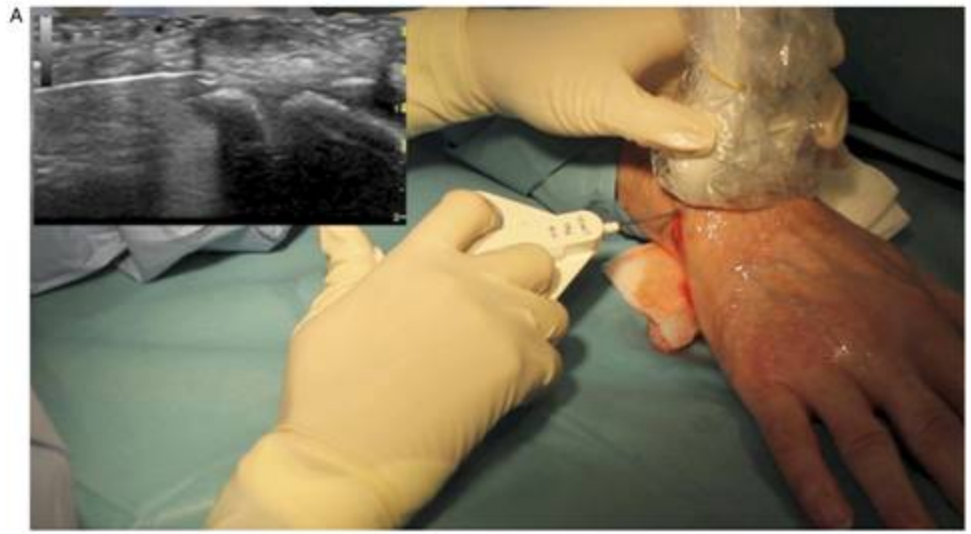
Arthritis Research UK

MRC Medical Research Council

NHS National Institute for Health Research

Ultrasound-guided synovial biopsy: a safe, well-tolerated and reliable technique for obtaining high-quality synovial tissue from both large and small joints in early arthritis patients

S Kelly,[1] F Humby,[2] A Filer,[3] N Ng,[2] M Di Cicco,[2] R E Hands,[2] V Rocher,[2] M Bombardieri,[2] M A D'Agostino,[4] I B McInnes,[5] C D Buckley,[2] P C Taylor,[6] C Pitzalis[2]



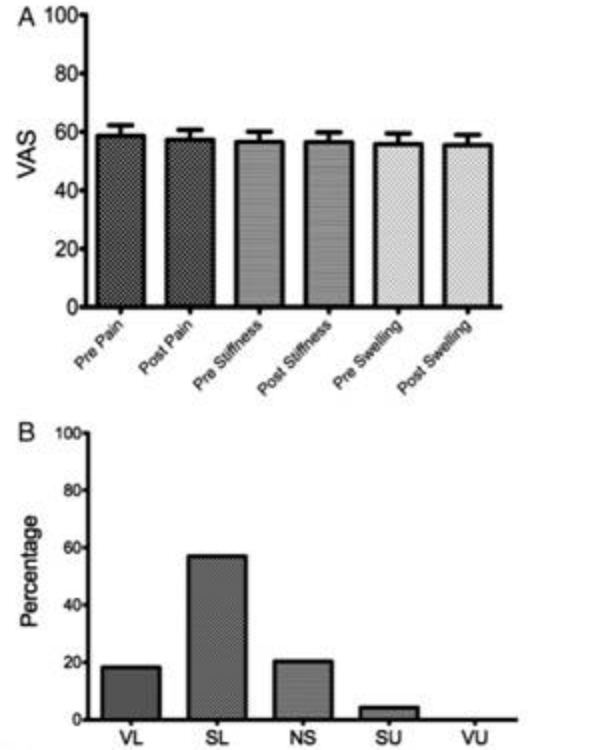
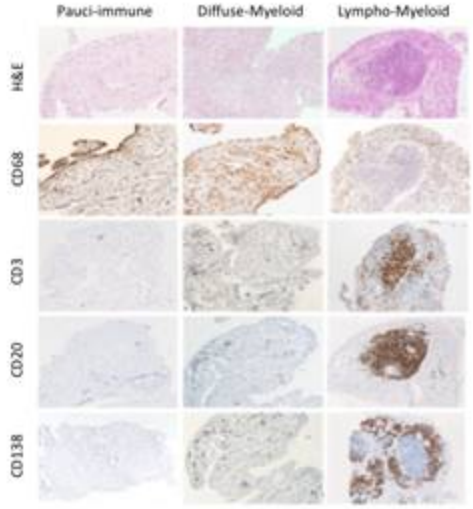


Figure 2 Ultrasound-guided synovial biopsy is a safe and well-tolerated procedure. (A) Patients were also asked to complete a visual analogue score assessing immediately prior to and following the procedure, joint pain, stiffness and swelling. No significant differences in any of the three variables preprocedure and postprocedure were reported (n=93). (B) At their postprocedure clinic visit 3–7 days following the synovial biopsy, patients were also asked to record how agreeable they were to having a subsequent synovial biopsy: very likely, somewhat likely, not sure, somewhat unlikely and very unlikely. Results are expressed as percentage of total patients (n=93).

Kelly S, *et al*. *Ann Rheum Dis* 2013;**0**:1–7. doi:10.1136/annrheumdis-2013-204603



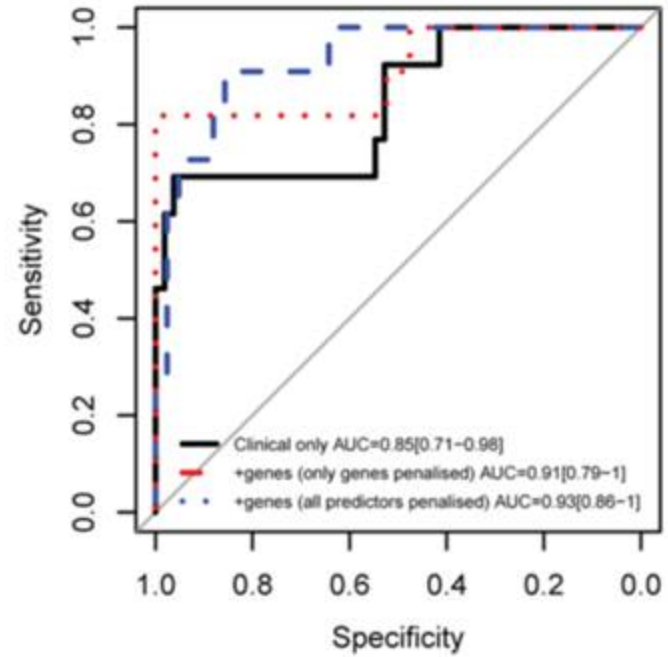
A

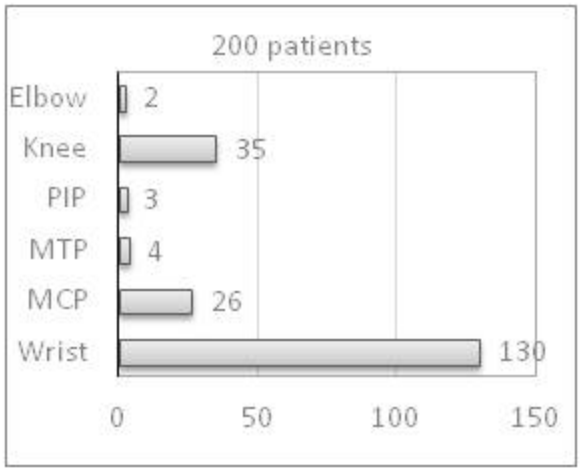
12 months (n=89)		Pauciimmune-fibroid/Diffuse-Myeloid n=55 (61.8%)	Lympho-myeloid n=34 (38.2%)	P value
SHSS	Erosions	0.49 (1.23)	0.71 (1.68)	0.759
	JSN	1.71 (3.66)	3.62 (4.96)	0.044*
	Total	2.2 (4.05)	4.32 (6.04)	0.068
ΔSHSS		0.44 (2.92)	0.85 (2.22)	0.042*
Progressors/non-progressors (ΔSHSS ≥1)		5/50	9/25	0.029*

TRANSLATIONAL SCIENCE

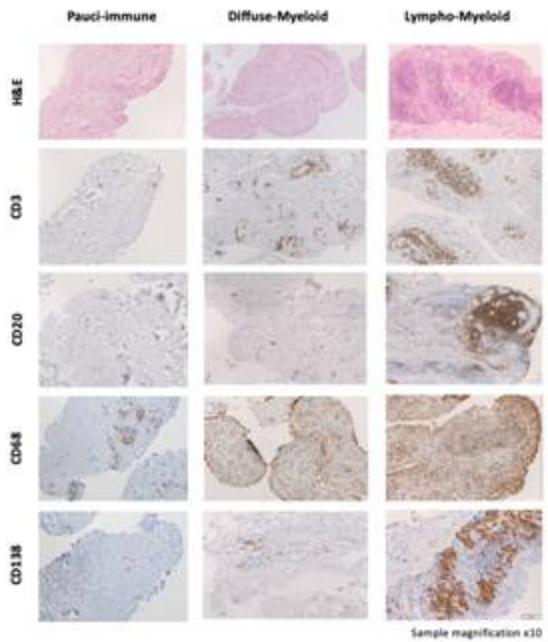
Synovial cellular and molecular signatures stratify clinical response to csDMARD therapy and predict radiographic progression in early rheumatoid arthritis patients

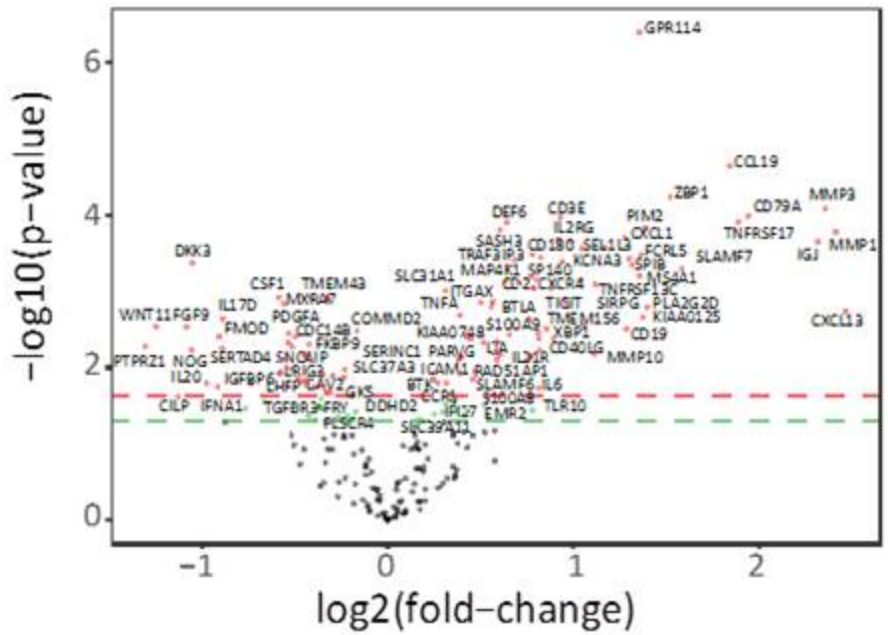
Frances Humby,[1] Myles Lewis,[1] Nandhini Ramamoorthi,[2] Jason A Hackney,[3] Michael R Barnes,[1,4] Michele Bombardieri,[1] A. Francesca Setiadi,[2] Stephen Kelly,[1] Fabiola Bene,[1] Maria DiCicco,[1] Sudeh Riahi,[1] Vidalba Rocher,[1] Nora Ng,[1] Ilias Lazarou,[1] Rebecca Hands,[1] Désirée van der Heijde,[5] Robert B M Landewé,[6,7] Annette van der Helm-van Mil,[5] Alberto Cauli,[8] Iain McInnes,[9] Christopher Dominic Buckley,[10] Ernest H Choy,[11] Peter C Taylor,[12] Michael J Townsend,[2] Costantino Pitzalis[1]

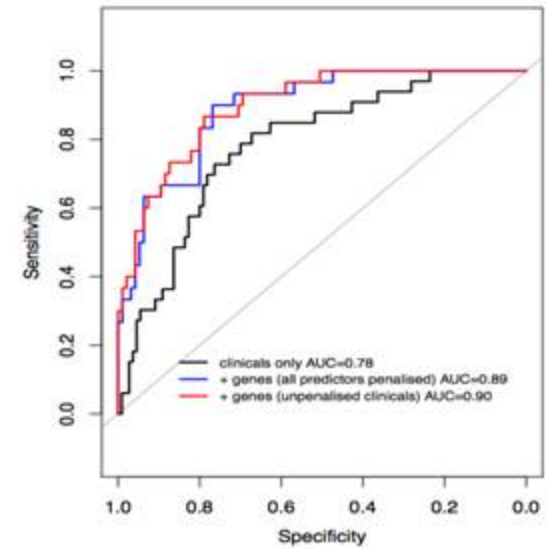




N 153	Pauci-immune N 44	Diffuse-Myeloid N 52	Lympho-Myeloid N 57	p-value
Symptomatic Treatment N 14	6 (42%)	6 (42%)	2 (14%)	<0.02*
csDMARDs N 101	30 (29%)	38 (37%)	33 (33%)	
Biologics +/- csDMARDs N 38	8 (21%)	8 (21%)	22 (57%)	







	All predictors penalised	Unpenalised clinicals
(Intercept)	-0.372	-3.572
Pathotype		-0.324
CRP	-0.015	-0.037
TJC		-0.061
DAS28	0.246	0.88
GPR114	0.242	0.295
IL8	0.26	0.265
CSF1	-0.08	-0.034
MMP3	0.051	0.047
LTB	0.017	
HIVEP1	-0.143	-0.182
IL20	-0.221	-0.239
UBASH3A	0.049	
MMP10	0.149	0.16
NOG		-0.038
IFNB1		-0.023

Lliso G, Humby F et al Annals of Rheumatic diseases August 2019 (in press)

PEAC (pathobiology of early arthritis cohort).
Rheumatoid arthritis (2010 EULAR/ACR Criteria)
Clinical, Histological and Molecular data
145 patients

csDMARDs

DAS28 <3.2
50 (34%)

DAS28 >5.1
Non-response to cDMARDs
40 patients (18%)

TNFi treatment
33 patients

7 patient TNFi stopped due to AE, recurrent or severe infections

12m Response Assessment

Eular Response

Good response

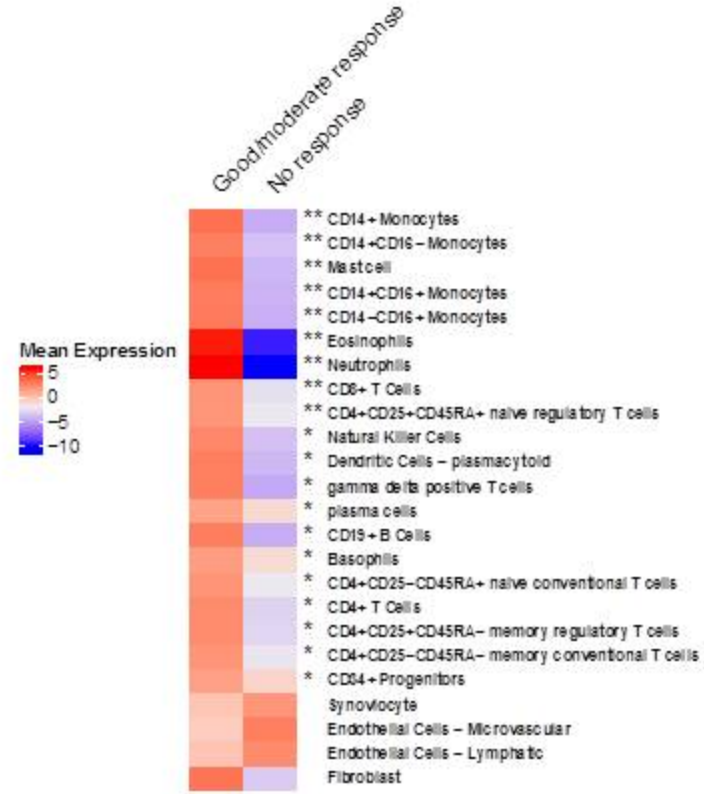
DAS28<3.2
DAS28 improvement >1.2
16 patients

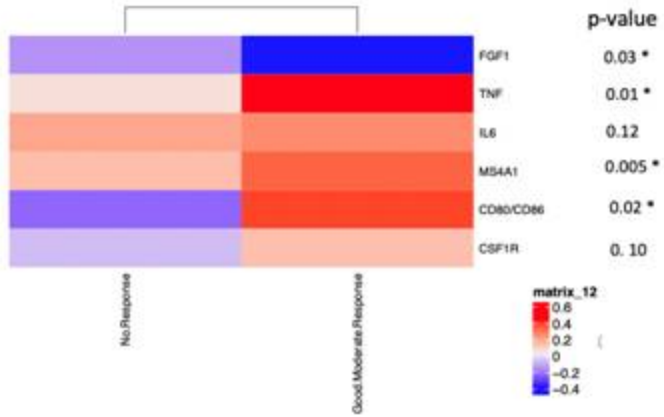
Moderate response

DAS28>3.2 and <5.1,
DAS28 improvement >0.6 and <1.2)
8 patients

No response

DAS28>5.1
DAS28 improvement <0.6
9 patients





Lliso, G. Humby F et al manuscript submitted

Importance of Stratified Medicine

Symptoms based approach

Diagnosis → Rheumatoid Arthritis → Treatment Decision → Treatment A → Treatment fails → Treatment B

Decreasing efficacy ! ££££

Stratified medicine approach

Clinical data
Deep phenotyping

Biological Samples
Transcriptomics

Integrative data analysis
Stratification into disease subcategories

Treatment A

Treatment B

Treatment C

Targeted Therapies

QUESTION: Clinical case 1

A 46 year old woman presents to the early arthritis clinic with new onset CCP+ve rheumatoid arthritis which is highly active (DAS>5.1). She is wealthy enough to self fund treatment. What would you start her on?

1. Tofacitinib

   0%
2. Methotrexate and steroids (po or im)

   0%
3. Adalimumab

   0%
4. Rituximab and methotrexate

   0%

Vote Now

QUESTION: Clinical case 1

A 46 year old woman presents to the early arthritis clinic with new onset CCP+ve rheumatoid arthritis which is highly active (DAS>5.1). She is wealthy enough to self fund treatment. What would you start her on?

1. Tofacitinib

   0%

2. ✓ Methotrexate and steroids (po or im)

   0%

3. Adalimumab

   0%

4. Rituximab and methotrexate

   0%

Clinical case 1

A 46 year old woman presents to the early arthritis clinic with new onset CCP+ve rheumatoid arthritis which is highly active (DAS>5.1). She is wealthy enough to self fund treatment. What would you start her on?

1. Tofacitinib
2. Methotrexate and steroids (im or po)
3. Adalimumab
4. Rituximab and methotrexate

QUESTION: Clinical case 2

A 25 year old man has highly active rheumatoid arthritis (DAS >5.1) and has failed on two conventional DMARDs (methotrexate and sulphasalasine). He continues on 15mg methotrexate weekly. He fulfills NICE criteria to start on advanced therapy. He is fit and well and has no comorbidities. Which of the following is likely to be the most effective treatment:

1. golimumab
2. certolizumab
3. abatacept
4. tofactinib
5. any of the above

Vote Now

QUESTION: Clinical case 2

A 25 year old man has highly active rheumatoid arthritis (DAS >5.1) and has failed on two conventional DMARDs (methotrexate and sulphasalasine). He continues on 15mg methotrexate weekly. He fulfills NICE criteria to start on advanced therapy. He is fit and well and has no comorbidities. Which of the following is likely to be the most effective treatment:

1. golimumab
2. certolizumab
3. abatacept
4. tofactinib
5. any of the above

Clinical case 2

A 25 year old man has highly active rheumatoid arthritis (DAS >5.1) and has failed on two conventional DMARDs (methotrexate and sulphasalasine). He continues on 15mg methotrexate weekly. He fulfills NICE criteria to start on advanced therapy. He is fit and well and has no comorbidities. Which of the following is likely to be the most effective treatment:

1. golimumab
2. certolizumab
3. abatacept
4. tofactinib
5. any of the above

QUESTION: Clinical case 3

A synovial biopsy should be routinely performed before starting advanced therapy to help guide therapeutic choice.

1. True

2. False

Vote Now

QUESTION: Clinical case 3

A synovial biopsy should be routinely performed before starting advanced therapy to help guide therapeutic choice.

1. True

✓ 2. False

Clinical case 3

A synovial biopsy should be routinely performed before starting advanced therapy to help guide therapeutic choice.

A. True

B. False

Summary

- Outcomes for patients with RA significantly improved driven by early diagnosis and advanced therapies
- Increasing therapeutic armamentarium for RA with little to differentiate between in terms of efficacy
- Co morbidities drive most in terms of drug selection
- Synovial pathobiological signatures are associated with disease outcome and therapeutic response
- Future of personalized approach to RA therapy in future

Acknowledgements

EMR Centre for Experimental Medicine & Rheumatology

NIHR | National Institute for Health Research

RESEARCH VERSUS ARTHRITIS

MRC Medical Research Council

Genentech A Member of the Roche Group

b+tlc BARTS CHARITY

Clinical, Laboratory and Biostatistician Team

Gloria Lliso-Ribera, Alessandra Nerviani, Felice Rivellese

Myles Lewis, Stephen Kelly, Michele Bombardieri

Mary Githinji, Rebecca Hands, Georgina Thorborn

Daniele Mauro, Katriona Goldmann, Giovanni Giorli, Lilliane Fossati