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A CLINICIAN'S CRITIQUE OF RA MODELS

Background

- Recent RA MTA ICERs
  - Companies – own drug versus competitor drugs
  - BRAM
- Why differences?
  - Model Structures & Operations
    - E.g. Cycle length
  - Clinical Parameters / Assumptions
- NICE 2002. Should current modelling be based on guidance or observed practice?

Clinical Parameters & Assumptions

- Population Characteristics
  - Finding the best fit for modelling problem?
- Treatment Sequences
  - Continuous DMARD use?
  - Modelling evolving practice
  - Class effects
  - Unknown consequences of modelled sequences
- Drug Monitoring, Dosing & Wastage
- Treatment Responses
  - Magnitude of benefits – data sources
  - Long term gains e.g. radiological damage, HAQ progression
  - Vexatious HAQs, Utilities and other nerdy aspects
  - Stopping Rules or Observed Continuation rates?
- Mortality & Treatment Hazards
  - Limitations of current modelling strategies

Preface: Treating the right patient with a DMARD(s)

- Classification criteria – recent changes
- Many patients with undifferentiated arthritis go into remission
- Prediction models are for populations and have limitations
- Early treatment is the standard of care not a mandate for DMARD use
- Clinic decisions
  - Professional judgements
  - Patient preferences
- A proportion of patients do badly even if treated optimally

Population Characteristics: Patients Entering RA MTA 2010 Models

	BMS	Roche (Ritx)	Sch-Plg	Wyeth	Abbott	BRAM
Source	ATTAIN	REFLEX	GO-AFTER	ReACT	BSRBR*	BSRBR (NICE)
Age	53	52	54	53	58	58
Dis Durn	12 yr	12 yr	12 yr	12 yr	11 yr	13 yr
HAQ	1.8	1.9	1.6	1.9	2.1	2.0
Steroids	70%	65%	-	77%	47%	45%
Previous DMARDs	-	2.6	2.8	5	4	4
CRP	46	37	~10	-	-	-

* Characteristics at start of 1st TNFi: Hyrich 2008 doi:10.1093/rheumatology/ken127

Treatment Sequences

- Current approaches – contemporary trials
  - UK practice & NICE guidance e.g. early TNFi use denied ?
  - TEAR study, BeSt study, Swefot trials, GUEPARD – Rx strategies
- Beyond first few DMARDs
  - Considerable uncertainty & variation but range wider than modelled
  - Divergence after failure of 1st TNFi
- All models assume continuous DMARD use
  - Incorrect – impact on modelling ?
  - Evolving practice – early use & DMARD withdrawal
  - But – late presentation relevant?
  - Earlier use of biologics
- Unknown clinical consequences of untried (but modelled) sequences
  - E.g. MTX/HCQ → TNFi (1) → TNFi(2) → rituximab → toc → abatacept

- 28 patients
  - 6 (21%) gained DAS improvement 0.6
  - 16 (57%) discontinued after ~ 10 months
- Toxicity
  - Pneumonia 2 (7%) patients
  - Erysipelas 1 patient (hospitalised)

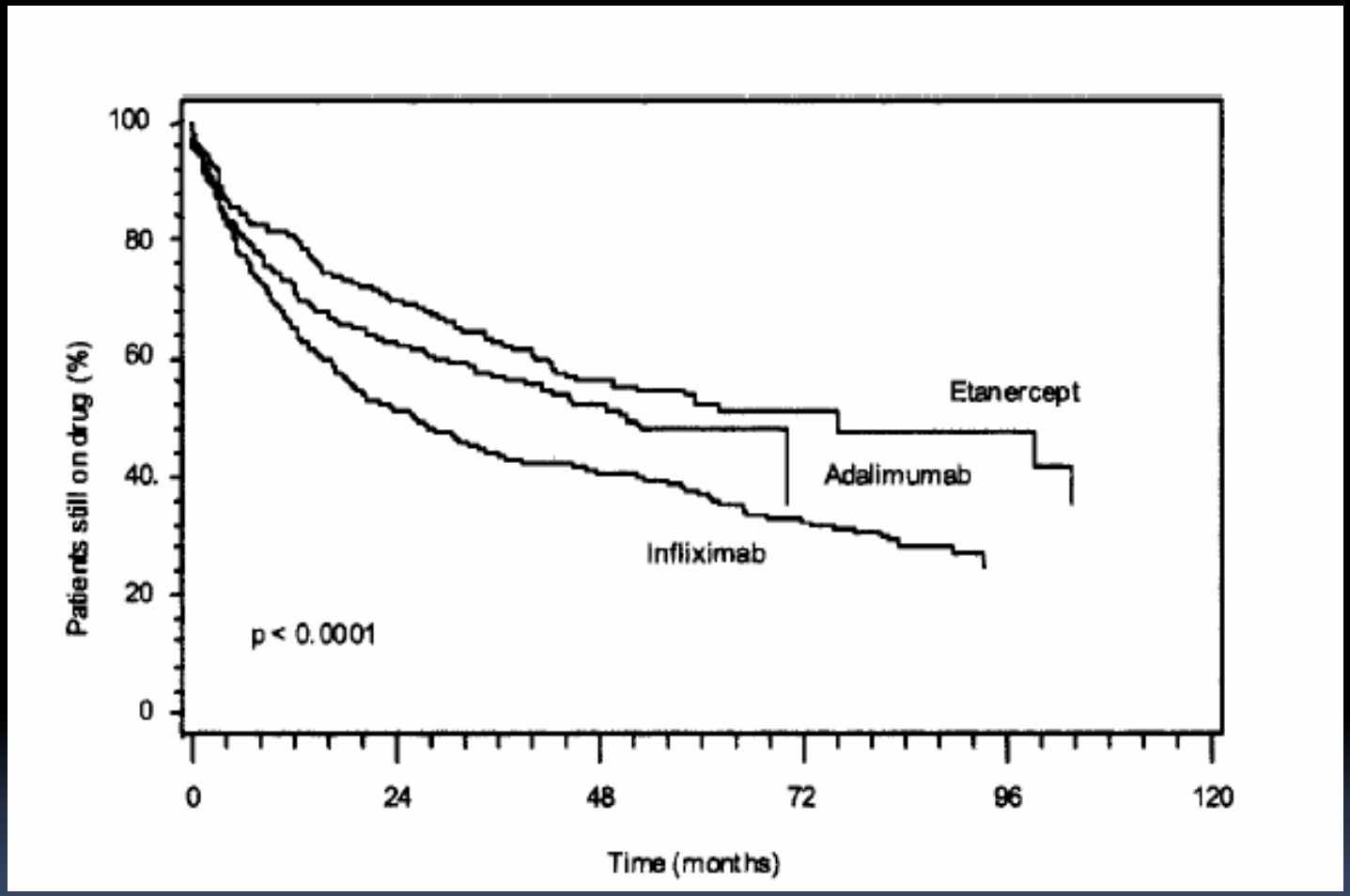
Walker UA et al. Rheumatology 2010doi:10.1093/rheumatology/keq258

Effectiveness of Late DMARDs

- Patients who do not respond to have MTX have resistant disease – fact?
  - Hence using std DMARDs has virtually no value
    - Especially if biologics have failed
  - In this situation the only drug that is likely to work is another biologic
- Evidence:
  - BeSt study – observational analysis
  - Trial data shows that MTX failures may respond to gold, ciclosporin or leflunomide.
  - Data on DMARD use after biologic failure limited

Class Effects: Are all TNFi the same?

- Differences in mechanism of action
- Lessons from IBD
- Potential for same in Seronegative arthritis?
- Head-to-heads
  - Do they matter?
  - Are they doable?
- Observational studies of continuation rates
- Potentially similar issues future biologics



Hetland ML, et al. A&R 2010. DOI 10.1002/art.27227

Drug monitoring, dosing & wastage

- Monitoring - Mostly appropriate
- Drug dosing variation
  - Rituximab frequency
  - TNF inhibitors
    - Vial Sharing
    - Dose escalation
      - May be ignored if you model guidance but :
      - 44% infliximab patients; 8% of adalimumab
    - Dose reduction

Treatment Responses

- Model population characteristics differ
  - Higher HAQ ↓ response;
  - Longer disease duration → ↓ DMARD response
- Determinants of responses & continuation in models:
  - ACR Responses
  - DAS thresholds
  - Observed Continuation rates

Response Criteria in Models

	Criterion	Comment
Abbott	ACR50	HAQ calculated from ACR response
BMS	HAQ ≥0.3	Continuation rates based on trials, observational studies, and & Barton et al. Source of 0.3?
BRAM	Observed Continuation	BSRBR & other observational studies
Roche	ACR20,50 & 70	HAQ calculated from ACR response.
Schering Plough	ACR response	ACR responses mapped to DAS28
Wyeth	HAQ	HAQ scores modelled to DAS28 ('decision point')

Individual Treatment Decisions, Thresholds & Rules

- Are population level outcomes relevant to individual decision making?
  - ACR criteria measure change
  - DAS measures change and status
  - Parameters for DAS / ACR vs. parameters used by clinicians
- Origin of DAS thresholds
  - Patients in whom therapy was being changed were studied.
  - Predictors of changed therapy identified
  - Used in trials - then used to as an instrument of regulation
- Problems of DAS measurement
  - Test-retest variability – Smallest detectable difference ~1.32
  - Disease fluctuation, ankle & foot disease
  - Poor correlation between physician & patient scores

DAS28 Scoring Inside the Clinic

- Prevailing belief that CE achievable by enforcing stopping rules:
- Potential Implications
  - Clinicians cannot be trusted;
  - That practice is sloppy & profligate in drug monitoring & prescribing
  - That an 'objective' DAS28 threshold subsumes clinical judgment
- Potential Consequences of Stringent Enforcement

Problems of Continuation Rates

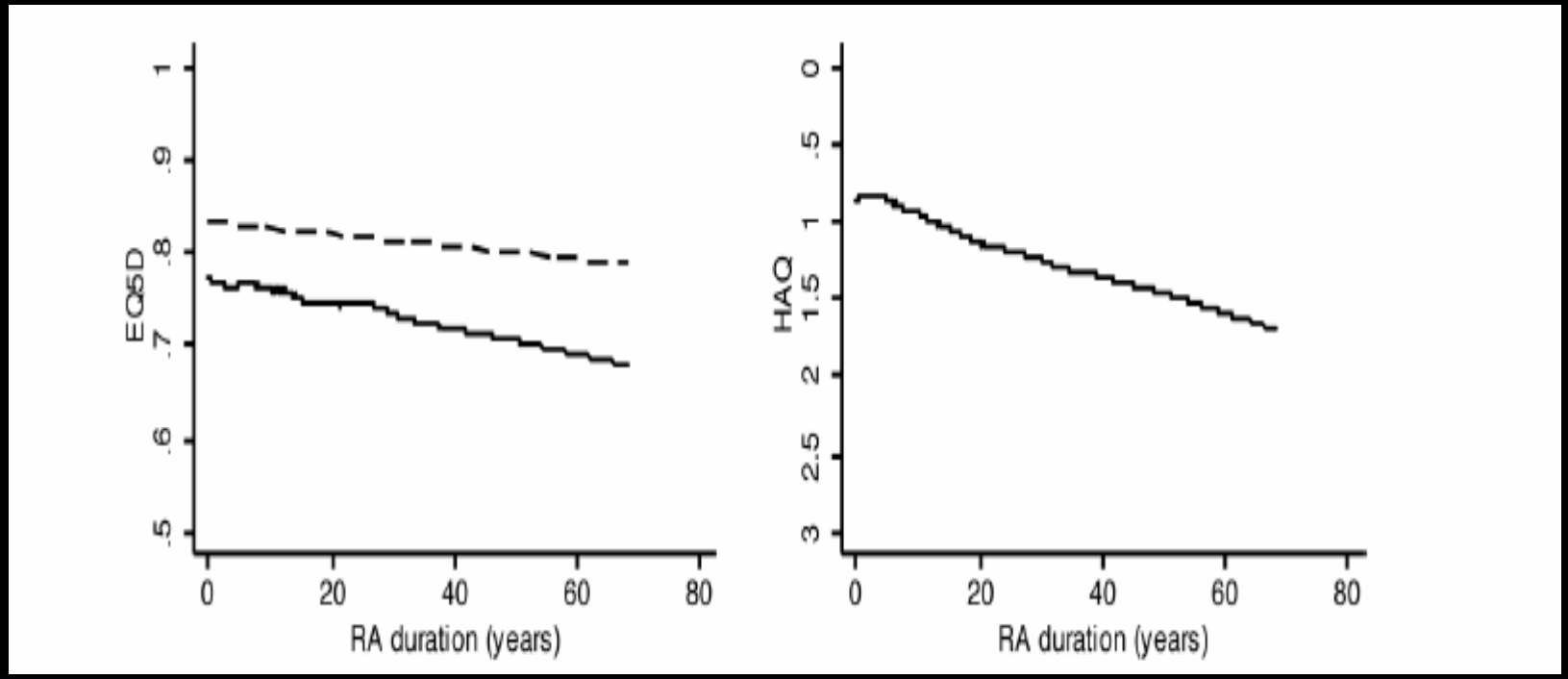
- Persistence because of limited future options
- Cohort effect

- Use of published data = modelling historical practice

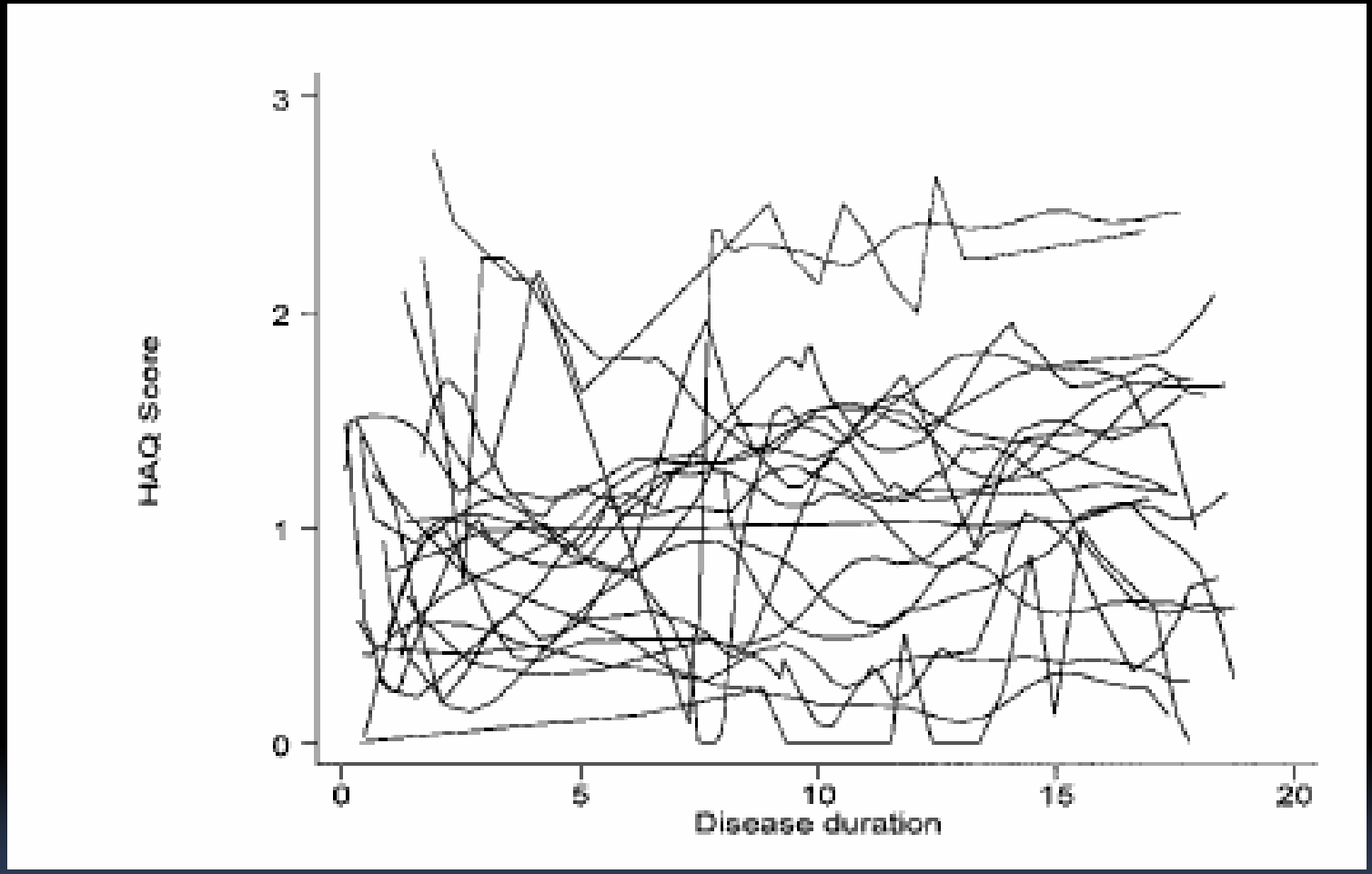
Physical impairment in time

Models showing favourable ICERs assume HAQ progression = 0 with sustained therapy.

- Is this justified?
  - Does therapy confer protection against normal ageing?
  - Does continued therapy mean absence of rheumatoid disease in all?
  - If no to both of these – disability inevitable but
    - Does it occur gradually or step-wise?
    - Do population curves mislead?



Wolfe and Michaud *Arthritis Research & Therapy* 2010, **12**:R35
http://arthritis-research.com/content/12/2/R35



HAQ patterns in individual patients….

'The model that self-reported physical disability, as measured by the HAQ, occurs as a function of disease acting over time does not fit the data well and is an inadequate model. ' Wolfe F. A&R 2000;43:2751.

HAQ Progression

Table 2 Annualized *observed rates* of progression of disability and loss of health status in rheumatoid arthritis

Variable	All patients (N = 18,485) Rate (95% CI)	Biologics never used (N = 10,265) Rate (95% CI)	Biologics ever used (N = 8,220) Rate (95% CI)
HAQ	0.013 (0.010, 0.015)	0.016 (0.013, 0.019)	0.010 (0.007, 0.013)
EQ-5D	0.001 (0.001, 0.002)	-0.000 (-0.001, 0.001)	0.002 (0.012, 0.003)

Wolfe and Michaud *Arthritis Research & Therapy* 2010, **12**:R35
http://arthritis-research.com/content/12/2/R35

Other Model Parameters 1

- SMR attributed to RA varies in models
  - Link to HAQ in some
  - RA multiplier varies in different models
  - Some models (e.g. Abbott) ↓ hazard ratio for TNFi treatment (0.95 ♂; 0.52 ♀) - confounding
- Hospitalisation
  - Hazard of Hospitalisation for RA varies:
    - Bed & day case facilities; iv steroid use; clinician
  - Data used in models
    - Guesswork : e.g.cost per unit HAQ (BRAM)
    - Historical data e.g. Abbott using NOAR data (inception cohort of 1989).

Other Model Parameters 2

- Joint Replacements
  - Relationship to HAQ – based on US data
  - Relevant to UK practice?
- Adverse Events
  - Some models have assumed costs to various types of AEs (e.g. BMS attributed £36 to a rash)
  - Much uncertainty
  - Relevance of recent data linking serious infections to TNFi therapy from BSRBR?

Summary

- Range of Clinical Parameters Needed
  - Choices of populations; treatment strategies; outcomes; assumptions
- Choices
  - Likely to have a greater influence on model outputs than model structure
- Aspects of modelling guidance versus clinical practice