An overview of models used in economic analyses of biologic therapies for arthritis

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Outline

- Set out a structure for comparing models
- Use this structure to compare alternative choices modellers have made
- Assess these alternatives in the light of the NICE methods guide.
- All statements and examples from my review of model descriptions: If I have mis-interpreted any models, I apologise!

Why do different models give different answers?

- Results from alternative models can be quite different
  - RA, 3rd line, ETA vs DMARD: £20K/QALY to £88K/QALY (NICE TA 130)
- These differences can arise because of:
  - Differences in the source or interpretation of data
  - Differences in models structure / assumptions
- Principles exist to judge alternative approaches, although more than one plausible answer may still exist.

Main areas for model comparison

- CEA model assumptions in arthritis:
  - Initial response to treatment (RCT data available)
  - Longer-term response if treatment continued (RCTs provide insufficient information)
  - Other assumptions - mortality, QoL, cost (specific to the decision context)

NICE 2008 Methods Guide

- Outcome measure
  - clinically relevant
  - Link to QALYs
  - Model values from systematic review
- Pre-specified evidence base with explicit selection criteria
- Treatment effects should be based on RCTs (preserving randomisation)

NICE 2008 Methods Guide

- Observational data can be used for:
  - Baseline event rates
  - Extrapolating from trial evidence to different populations and long-term outcomes
- Should also be pre-specified and systematic
- Presentation should include
  - Reference case + additional analyses to explore alternative plausible assumptions
  - Probabilistic results (allowing for uncertainty in model parameters

Initial Response – What are the main model assumptions?

- Choice of outcome measure(s)
  - should be clinically relevant and translatable to QoL
- Derivation of treatment effect
  - Treatment effects should come from the systematic review (all relevant trials, relative treatment effects).
- Switching rules
  - should reflect guidelines and best practice

Initial Response – Choice of measure

- Various measures have been used:
  - ACR20/50/70 (e.g. Brennan 2004),
  - Absolute change in HAQ (e.g. Wyeth submission to TA130), % change in HAQ (e.g. BRAM in TA130)
  - EULAR / DAS (BSR submission to TA130)
- This choice can have implications for
  - Selection of evidence (e.g. UCB in TA186 exclude trials that do not provide ACR20 at 3/6 months)
  - Need for supplementary (unpublished) data
  - Prediction of short-term treatment failure
- Use of mapping functions can improve model flexibility

Initial Response – Source of evidence

- Different data sources for the same parameter
  - E.g. HAQ change for Etanercept, 1st line
    (BRAM TA130 uses ERA, Wyeth use TEMPO)
- Different ways of using multiple trials:
  - Absolute response taken from separate trials
    (Brennan 2004 use Moreland 1999 for Etanercept, Anderson 2000 for Gold)
  - Absolute response taken from the same trial
    (Wyeth use TEMPO for both Etanercept and Methotrexate)
  - Relative treatment effects combined through formal synthesis

Initial response – switching rules

- Treatment is usually withdrawn if short-term (6 month) response is inadequate

- Models reflect this in different ways:
  - All ACR non-responders defined as treatment failures (Brennan 2004, 50% ETA failure rate from Moreland 1999)
  - Failure rate estimated from a separate data source (BRAM TA130, 7% ETA failure rate from Geborek)

Longer-term outcomes – What are the main model assumptions?

- Models include parameters for:
  - Time until biologic fails to control disease progression (or is withdrawn due to SAE)
  - Rate of decline in health status on treatment
  - Rebound on treatment failure
- These may draw on observational data:
  - Pre-specified and systematically found
  - Reference case should avoid treatment effects based on such data
- Alternative assumptions should be explored

Duration of treatment

- Treatment duration, source of data:
  - Assume limited to trial follow-up (Kobelt 2005)
  - Extrapolate from trial (Wyeth TA 130)
  - Extrapolate from routine data, assume equal for all biologics (UCB TA186)
  - Extrapolate from routine data, allow differences between biologics (BRAM TA130)
- Extrapolation may assume hazard rate (% failing per month) is constant (York TA104) or varying over time (BRAM TA130)
- Can lead to significant differences e.g. mean time on etanercept 3 yrs (UCB TA186) vs 15 yrs (BRAM TA 130)

Progression on treatment

- Progression on treatment assumed to be
  - the same for all treatments (BRAM TA130)
  - differ based on trial data (Wyeth TA130) or routine data (Brennan 2004).
- Withdrawal rebound may be
  - equal to initial improvement (Brennan 2004),
  - return to disease state in the absence of treatment (Kobelt 2005), or
  - Less than initial improvement (Wyeth TA130)

Other model assumptions

- Mortality:
  - Models tend to adjust life expectancy for RA.
  - Many vary the adjustment by disease severity (e.g Kobelt 2005)
- Quality of Life
  - usually mapped from HAQ using observational data
  - mapping functions similar but not identical e.g. BRAM imposes a higher QALY loss per HAQ than Wyeth / Abbott in TA130

Other model assumptions

- Resource use included:
  - Varies from drug cost only (e.g. BRAM) to including a broad range of direct and indirect costs (e.g. Kobelt)
  - Some studies calculate health utilisation as a function of HAQ (Abbott TA130).
- NICE methods guide describes costs to include in reference case

Individual Patients vs Single Cohort

- Models can either model individual patient histories (BSR/Sheffield TA130) or represent patients as a single cohort (York TA104)
- Cohort models base analysis on a ‘typical’ patient, can represent heterogeneity by varying the definition of typical
- Individual patient models are more flexible, but add complexity (probabilistic and VoI difficult).

Summary

- Models differ because they
  1. Use different data sources
  2. Draw information from them differently
  3. Make different structural assumptions

- Methods guidance can improve agreement on choice of data and method of synthesis

Summary

- Structural assumptions should be clinically plausible
- Additional information may help in distinguishing between assumptions.
- VoI methods can tell us which information to collect.