Developing a therapeutic range and predicting response to biologics in patients with psoriasis:

a multicentre prospective observational cohort study

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Background

- Biologic therapies have transformed treatment in psoriasis
- Treatment response is variable
- Biologics are high cost drugs - the NHS spent >£415 million on adalimumab in 2016
- Therapeutic drug monitoring is well established to optimise treatment outcomes in medicine, and has the potential to reduce costs
- Fundamental to therapeutic drug monitoring is the requirement of a clinically valid therapeutic range

Aims

1. To determine a **therapeutic range for adalimumab**
2. To determine whether measurement of **early drug levels** predicts treatment response

Study Design

- Prospective observational cohort study
- Large multi-centre UK study (n=60); dermatology specialist care setting
- All patients **registered in BADBIR**
- **Biological samples** - blood for DNA, RNA, serum
- **4600 patients** and **>16,000 samples** collected
- Long-term **safety** of biologic treatments for psoriasis
- Baseline and follow-up **clinical information** eg. medical history, previous treatment, length and severity of condition
- **Outcome** data (Psoriasis Area and Severity Index (PASI), Dermatology Quality of Life Index (DLQI), Physician Global Assessment (PGA))

Derived Datasets

- Focused on first year of treatment
- **Primary treatment response PASI75**
- **Secondary outcomes: PASI90, PASI≤1.5**

Results

1.a) Therapeutic range for adalimumab – minimum/maximum levels

The minimally effective drug level of ≥3.3 µg/ml was identified for PASI75 response

- sensitivity: 80%
- specificity: 57%
- AUC: 0.73 (95%CI: 0.67-0.79)
- PASI75 rate
 - where drug <3.3 µg/ml=44%
 - where drug ≥3.3 µg/ml=81%
- Clearly discriminates between responders and non-responders

- Drug levels ≥4.6 µg/ml were not associated with further improvement in PASI change
- Large variability - even at high drug levels some patients do not achieve PASI75

1.b) Therapeutic range for adalimumab – target level

- **Target drug level of 7 µg/ml** required to achieve 80% probability of PASI75: **81% (95% CI: 76-86%)**
- **The target drug level of 7 µg/ml** gives a **50% (95% CI: 44 to 56%)** population averaged probability of PASI90 response*

2. Early drug levels as a predictor of 6-month treatment response

Summary of findings

- Minimal effective drug level of 3.3 µg/ml indicates a threshold below which treatment modification should be considered
- A target drug level of 7 µg/ml identifies a patient population that might benefit from dose minimisation eg. 16.6% of all samples (n=380) correspond to a PASI90 response and have a drug level ≥7
- External validity likely to be excellent
- Pragmatic serum samples opposed to trough level sampling in a real-world dataset

Conclusions

- We provide strong evidence to support:
 - proactive measurement of drug levels
 - identification and individualisation of target drug levels early in treatment course, in order to optimise clinical utility
- Variability in response is largely explained by drug level, but other factors may be important
- Drug levels should be taken into account when searching for biomarkers of treatment response