SEQUENTIAL TNF-α INHIBITORS AND NON BIOLOGIC DMARDS – ANALYSIS OF THE NATIONAL DATABANK FOR RHEUMATIC DISEASES.

NICE DECISION SUPPORT UNIT

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1. Introduction

The Decision Support Unit (DSU) has reviewed evidence of the effectiveness of sequential TNF-α inhibitors[1] and the effectiveness of non biologic DMARDs[2] in the same population. Evidence of the latter in particular is limited. Therefore, in order to provide additional information that may be useful to this appraisal, particularly in order to provide alternative estimates to those provided by the UK British Society for Rheumatology Biologics Registry (BSRBR)[3], the US National Databank for Rheumatic Diseases (NDB) was asked to conduct certain analyses. Given that the use of TNF-α inhibitors, including sequential use, is more widespread in the US than in the UK, the NDB provides a potentially important source of information. In particular, switchers in the UK BSRBR are likely to be the more severe patients since they are "early" switchers. These may not be representative of those who will switch in the future and it may be the case that the NDB provides a more realistic view of potential future NHS practice than the BSRBR. These analyses were not able to be completed at the time of the previous DSU reports. Therefore, this separate report describes these analyses.

The National Databank for Rheumatic Diseases (NDB) is a not-for-profit rheumatic disease research databank in which patients complete detailed self-report questionnaires at 6 month intervals [Wolfe and Michaud, 2005]. Patients in the NDB are recruited from two sources: 1) non-selected patients from the practices of US rheumatologists and 2) patients enrolled as part of pharmaceutical company sponsored registries. Eligible patients in this study were those with RA who had completed a biannual survey for events occurring between July 1 1998 and December 2007. Patients were referred by 1,137 U.S. rheumatologists dispersed throughout the US. More than 90% of rheumatologists were in private practice and not full time university physicians. The diagnosis of RA was made by the patients' rheumatologists.

At each assessment, patients describe all medications used. Demographic variables were recorded including sex, age, and ethnic origin. Patients also complete the Health Assessment Questionnaire Disability Index (HAQ-DI), EuroQol, SF-6D and a VAS QOL scale.

The NDB attracts participants that are not necessarily representative of the RA community. NDB participants tend to be from higher income backgrounds, are less likely to come from an ethnic minority and are better educated than the general US RA population which in turn may differ from the UK RA population. Nevertheless, the NDB is the largest patient reported databank for rheumatic diseases in the US and one of the richest data sources available for the study of RA patients.

2. Analyses

Analyses performed by the NDB were designed to provide information in the form used by the BRAM cost effectiveness model, namely mean HAQ improvement over 12 months[4]. We also ran simple linear regressions to explore the impact of baseline HAQ, age, sex and disease duration on HAQ improvement.

For the analysis of traditional DMARDs the following patients were included:

- had taken a TNF-α inhibitor previously and stopped for any reason other than adverse events
- have a HAQ measurement taken within three months of stopping the TNF-α inhibitor
- are using any of the following DMARDs at the time of the follow up measure and which they were not taking at the time of quitting the TNF- α inhibitor:
    - methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, ciclosporin, azathioprine, penicillamine, injectable gold.

For the analysis of sequential TNF–α inhibitors, the analyses used the same inclusion criteria but considered patients who switched to etanercept, adalimumab or infliximab rather than non biologic DMARDs.

3. Results

3.1 DMARDs

A total of 275 patients were included in the DMARD analysis. Details are in Table 1. The mean HAQ change over 1 year is zero (95% CI -0.05 to 0.05).

Table 1: HAQ improvement and characteristics of patients switching to DMARDs

Variable	N	Mean	SD	Min	Max
HAQ at 1 year	275	1.41	0.67	0	2.75
Baseline HAQ	275	1.4	0.67	0	3
HAQ improvement	275	0	0.41	-1.75	2.5
Age (years)	275	62	11.88	27.46	89.17
Sex (% male)	275	14.91			
Disease duration (years)	275	17.45	11.32	2.16	60.22
Lifetime DMARD (running count)	275	4.01	1.79	1	9
Lifetime biologic use (running count)	275	1.66	0.92	0	4
Lifetime DMARD & biologic use (running count)	275	5.67	2.15	2	12

Table 2 shows the results of a linear regression of baseline HAQ, age, sex and disease duration on HAQ improvement. A lower baseline HAQ is associated with a greater improvement in HAQ. The coefficient for males is also negatively correlated with HAQ improvement (p=0.09).

Table 2: Determinants of HAQ improvement in patients that switched to DMARDs

	Coef.	Std. Err.	t	P>|t|	95% CI	
Baseline HAQ	-0.19	0.04	-5.29	0.00	-0.27	-0.12
age	0.00	0.00	0.76	0.45	0.00	0.01
sex (male)	-0.12	0.07	-1.73	0.09	-0.25	0.02
disease duration (yrs)	0.00	0.00	-0.05	0.96	0.00	0.00
_cons	0.20	0.14	1.42	0.16	-0.08	0.48

3.1.1 Analysis by individual DMARD

The BRAM assumes that methotrexate and sulfasalazine come before the first TNF-α inhibitor. Current NICE guidance recommends that a first TNF-α inhibitor is only used after failure of at least two DMARDs including methotrexate[5]. Therefore, the same analyses as above were performed by individual DMARD. However, the numbers of patients satisfying the criteria for each DMARD were too low for some DMARDs. The mean HAQ change for methotrexate, sulfasalazine, leflunomide and Hydroxychloroquine is shown in table 3.

There are differences between the mean changes in HAQ across the different DMARDs, with a range of 0.07 (worsening) to -0.05 (improvement), although these are not statistically significant.

Table 3: Mean HAQ improvement over 12 months by DMARD

DMARD switched to	n	mean	sd	se	low	high
Methotrexate	124	0.02	0.43	0.04	-0.06	0.10
Sulfasalazine	45	-0.05	0.36	0.05	-0.16	0.06
Leflunomide	64	-0.04	0.42	0.05	-0.14	0.06
Hydroxychloroquine	46	0.07	0.45	0.07	-0.06	0.20

3.2 Sequential TNFs

Table 4 shows the mean HAQ improvement for patients switching to sequential TNF-α inhibitors. There is a small improvement in mean HAQ over 1 year of 0.04 (95% CI, -0.09 to 0.01). There are no significant differences between patients that switched to a DMARD with those that switched to a TNF-α inhibitor. Table 5 shows that the coefficients for baseline HAQ and for males are negatively related to HAQ improvement.

Table 4: HAQ improvement and characteristics of patients switching to TNF-α inhibitor

Variable	N	Mean	SD	Min	Max
HAQ at 1 year	284	1.3	0.69	0	2.88
Baseline HAQ	284	1.34	0.65	0	2.75
HAQ improvement	284	-0.04	0.45	-1.75	1.63
Age (years)	284	59.41	12.88	25.68	88.58
Sex (% male)	284	16.2			
Disease duration (years)	284	17.13	11.13	1.51	57.01
Lifetime DMARD (running count)	284	3.94	1.68	1	10
Lifetime biologic use (running count)	284	1.98	0.84	1	5
Lifetime DMARD & biologic use (running count)	284	5.93	2.02	2	13

Table 5: Determinants of HAQ improvement in patients that switched to TNF-α inhibitor

	Coef.	Std. Err.	t	P>|t|	95% CI	
Baseline HAQ	-0.18	0.04	-4.35	0.00	-0.26	-0.10
age	0.00	0.00	0.17	0.86	0.00	0.00
sex (male)	-0.15	0.07	-2.08	0.04	-0.29	-0.01
disease duration (yrs)	0.00	0.00	1.30	0.20	0.00	0.01
_cons	0.15	0.13	1.17	0.24	-0.10	0.40

4. Discussion and limitations

Data collection with the NDB occurs every six months as is the case with the BSRBR. Observations therefore do not coincide with the timings of medication changes. The NDB is an observational database and therefore patients are not selected at random for particular treatments. In addition to general issues that this may raise about the nature of the patients included in these data, in particular it must be recognised that there may be a tendency for patients to leave the NDB when disease control becomes poor.

In general, the results show that HAQ shows little change in those that switch to non biologic DMARDs after failure of a TNF-α inhibitor. This may vary by individual DMARD.

For those that switch to another TNF-α inhibitor, a relatively small improvement is demonstrated. It is worth noting that the mean improvement is lower than that evident in the BSRBR analysis which showed a mean change of 0.12 (95% CI 0.07 to 0.17). Although the difference between the two data sources is not statistically significant it is interesting that this is unlikely to be due to the fact that the NDB population is less severe than the BSRBR population. Both sets of analyses identified a negative correlation between baseline severity and improvement. It is also worth noting that the BSRBR analysis was confined to patients that failed to respond within 12 months of starting the first TNF-α inhibitor. The NDB analysis is not restricted to these primary non responders but also includes those that switch due to loss of efficacy.

References

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