

1. Executive summary

Introduction

This submission addresses the issues raised during the previous appeals of the appraisal of sequential TNF- α inhibitor treatment. This submission also includes new data which has become available since the previous appraisal of this topic and reflects new treatment guidelines. We therefore request, that based on the evidence presented in this document, sequential use of TNF- α inhibitors should be recommended for the treatment of rheumatoid arthritis.

Rheumatoid Arthritis (RA) is a lifelong progressive condition which has a substantial impact on a patient's life, as well as on health care budgets. The recent report by the National Audit Office (NAO) on services for people with RA recommends that once diagnosed, people with RA require close management to maintain tight control of the disease, optimise treatment, and to improve long-term prognoses.¹ This is also supported by the recently published NICE clinical management guidelines (CG79).² These state that the medical management of RA should focus on the modification of the disease process, aiming to halt radiological progression and the resulting functional impairment and disability, as well as the relief of symptoms.

These treatment goals have now been included in numerous treatment guidelines, e.g. the British Society of Rheumatology (BSR), EULAR.^{3, 4} In order to achieve the treatment goals, these treatment guidelines recommend the use of a second TNF- α inhibitor.

The introduction of TNF- α inhibitors has revolutionised the treatment of RA. However not all patients have an adequate response to their first TNF- α inhibitor. Some patients stop treatment due to adverse events, and some experience a gradual loss of effectiveness over time. Those patients with secondary treatment failure or those developing adverse events gained the highest HAQ improvements, as compared with patients who do not show an adequate response. It is not possible to predict how patients will respond to individual drugs. Despite targeting the same cytokine, given the differences in mechanism of action and administration, it is rational to use different TNF- α inhibitors in the same patient.

Whilst conventional Disease-Modifying Anti-Rheumatic Drugs (DMARDs) address the relief of symptoms, only biological agents have been shown to effectively halt the progression of the disease, and achieve remission.⁵⁻⁷

Current NICE guidance (TA130) recommends that prior to starting a TNF- α inhibitor patients should have failed two conventional DMARDs, including MTX. Evidence from the BEST study demonstrates that patients whom have failed MTX are unlikely to respond to another conventional DMARD.^{8, 9} Additionally, data from the BSRBR shows that patients reverting to conventional DMARD therapy after the failure of a first TNF- α inhibitor experience no improvement of their disease.¹⁰

Rituximab has been proposed as an alternative to a second TNF- α inhibitor; however it is important to realize some important clinical limitations of this drug which question its appropriateness for many patients that have failed a first TNF- α inhibitor. Firstly,

rituximab has only been licensed for the treatment of RA for a limited time compared to TNF- α inhibitor agents and the available safety data is consequently limited compared to the evidence base around the TNF- α inhibitor agents. In particular the safety of further treatment with biological agents or DMARDs in B-cell depleted patients that failed rituximab is poorly understood.

Furthermore rituximab is only licensed in combination with MTX whereas a significant number of patients cannot tolerate MTX and TNF- α inhibitors are licensed either as monotherapy, as well as combination (with MTX) treatments.

Whilst there is convincing evidence that TNF- α inhibitors can halt radiographic progression of RA, the evidence supporting rituximab's effectiveness in achieving radiographic remission is less strong⁵⁻⁷ It is in this context important to highlight that patients are only retreated with rituximab once they become symptomatic. This leads to a lack of control of the sub-clinical inflammatory process and its deleterious effects on joints. Furthermore, rituximab is only effective in half of the patient population. There are concerns about the lack of efficacy of rituximab in sero negative RA patients. Finally, there are concerns about the occurrence of progressive multifocal leukoencephalopathy (PML) in patients treated with rituximab.¹¹

The previous considerations by the Institute concluded that sequential TNF- α inhibitor use should not be approved on the basis of a lack of randomised control trial (RCT) data resulting in uncertainty of the estimates of cost-effectiveness. However, given that RA is a life long disease, we believe the use of a second TNF- α inhibitor is required to enable a higher proportion of patients to achieve the goals of therapy, laid out in the recommendations by the NAO, BSR, EULAR, as well as in the Institutes own clinical management guidelines.

Clinical data

There are is a growing body of published evidence supporting the sequential use of TNF- α inhibitors. Additional RCT data has become available with the golimumab GO-AFTER trial. A wealth of observational data further supports the RCT evidence. This provides a substantial database for this appraisal.

In last year's Harveian Oration, delivered at the Royal College of Physicians, Professor Sir Michael Rawlins argued that whilst RCTs, long regarded at the 'gold standard' of evidence, their appearance at the top of "hierarchies" of evidence is inappropriate. He pointed out that observational studies are also useful and provide an important source of evidence about both the benefits and harms of therapeutic interventions. Reliance on RCTs should be replaced by a diversity of approaches that involve analysing the totality of the evidence-base.¹²

Cost-effectiveness

In the original appeal before the publication of TA130, the Institute were asked to consider the impact of a wider range of clinical effectiveness on the cost-effectiveness of a second TNF- α inhibitor vs. conventional DMARDs. We have provided this analysis in place of a base case (see Table 1).

Summary table 1: Impact of changes in HAQ on the cost-effectiveness of a 2nd TNF- α inhibitor vs. conventional DMARDs.

		Effectiveness of DMARD						
		0	-0.025	-0.05	-0.075	-0.1	-0.125	-0.15
Effectiveness of TNF	-0.15	£ 20,422	£ 20,422	£ 20,422	£ 20,422	£ 20,422	£ 31,141	£ 31,141
	-0.26	£ 16,180	£ 16,180	£ 16,180	£ 16,180	£ 16,180	£ 20,517	£ 20,517
	-0.31	£ 16,180	£ 16,180	£ 16,180	£ 16,180	£ 16,180	£ 20,517	£ 20,517
	-0.4	£ 15,294	£ 15,294	£ 15,294	£ 15,294	£ 15,294	£ 17,748	£ 17,748
	-0.41	£ 15,294	£ 15,294	£ 15,294	£ 15,294	£ 15,294	£ 17,748	£ 17,748
	-0.44	£ 15,294	£ 15,294	£ 15,294	£ 15,294	£ 15,294	£ 17,748	£ 17,748
	-0.48	£ 15,294	£ 15,294	£ 15,294	£ 15,294	£ 15,294	£ 17,748	£ 17,748
	-0.51	£ 14,501	£ 14,501	£ 14,501	£ 14,501	£ 14,501	£ 16,410	£ 16,410
-0.55	£ 14,501	£ 14,501	£ 14,501	£ 14,501	£ 14,501	£ 16,410	£ 16,410	

Our economic analysis also evaluates the cost-effectiveness of a second TNF- α inhibitor compared to the use of rituximab.

The cost-effectiveness of a second TNF- α inhibitor compared with rituximab is £16,225/QALY..

As highlighted in the earlier single technology appraisal of rituximab, a deterioration of HAQ by 50% whilst on rituximab treatment, would lead to a further drop of the ICER for a second TNF- α inhibitor.

Conclusion

Patients who fail initial treatment with a TNF- α inhibitor have limited treatments options available, which can result in suboptimal disease management.

This submission demonstrates that the sequential use of TNF- α inhibitors is not only clinically appropriate but also represents a cost-effective approach to the management of RA, and is thus an appropriate use of NHS resources.

Wyeth therefore requests that the Institute recommends the sequential use of TNF- α inhibitors.

Executive summary references

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