Guidelines for initiation of anti-tumour necrosis factor therapy in rheumatoid arthritis: similarities and differences across Europe

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Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease. In the majority of patients the course is progressive and leads to destruction of joints, functional disability, reduced quality of life and increased morbidity and mortality. Advances in treatment for RA have been associated with an improvement in the health status of patients with RA in recent years.[1] While the management of RA varies widely across Europe,[2] the underlying pathophysiology does not differ between countries. A cross-sectional comparison of patients with RA in 15 different countries (largely European) revealed great variation in the drug management of patients with RA, including the delay in starting a disease-modifying antirheumatic drug (DMARD) ranging from <6 to >12 months, use of methotrexate (<80% of patients in the UK and Serbia had received methotrexate) and use of biological agents (>40% in France and Ireland vs. <10% in Serbia and Poland).[3] It is also noteworthy that disease activity scores varied and were highest, on average, in Serbia and Poland.[3]

Although tumour necrosis factor (TNF) inhibitors have undoubtedly significantly advanced the treatment of RA, they are a higher cost treatment option and may not be suitable for all patients.[4] Hence, guidelines have been developed in order to assist the appropriate use of TNF inhibitors within individual countries.

In order to establish the level of access to TNF inhibitors across Europe, European guidelines were translated and reviewed with regard to their similarities and differences in the recommended criteria for the initiation of TNF inhibition. Particular attention was paid to recommended duration of disease and prior treatment with DMARDs, as well as disease activity levels.

The guidelines selected for inclusion were those from Belgium,[5] Czech Republic,[6] Denmark,[7] France,[8 9] Germany,[10] Italy,[11] Romania,[12] Spain,[13] Sweden[14] and the UK.[15] These were chosen to provide a fair geographical spread of countries, including countries with differing population densities and different levels of TNF inhibitor usage. Table 1 provides an overview of the recommendations made in these guidelines.

Duration of disease prior to initiation of anti-TNF therapy

It is clear that the duration of disease prior to the recommended initiation of TNF inhibitors is highly variable. The general consensus from national guidelines suggests that TNF inhibition could be started between 3 and 6 months following confirmed diagnosis of RA and failure of treatment with, usually, two DMARDs (including methotrexate). However, in the UK and Czech Republic, at least a year needs to elapse from RA diagnosis to TNF inhibitor initiation unless the patient cannot tolerate DMARDs, in which case it is possible to start treatment after only a few months.[6 15] This is in dramatic contrast to the Spanish guidelines, which suggest the theoretical possibility (although highly unlikely) of initiating TNF inhibition prior to a confirmed diagnosis of RA, if there is a high probability of RA in initial stages with especially aggressive progression suspected.[13] While the British Society for Rheumatology (BSR) guidance acknowledges the existence of evidence for the benefit of TNF inhibitors in patients with early RA and patients that are DMARD naïve, it does not recommend this approach.[15] A recent editorial regarding the need to update the BSR guidelines suggests that the reasons are financial and acknowledges that the UK BSR guidelines are out of kilter with other national guidelines.[16]

There is a growing body of evidence to suggest that treatment with disease modifying agents should be initiated early in the course of the disease. Importantly, Nell *et al* investigated the effects of delays to the initiation of DMARD therapy on long-term outcomes for patients with RA.[17] By comparing two groups of patients, one with a median symptom duration of 3 months and another with a median symptom duration of 12 months, they established that very early therapy provided significant improvements in disease activity, joint destruction and functional outcome. Furthermore, these differences were most apparent within the first 3 months of treatment, suggesting a ''window of opportunity'' in very early disease to rapidly halt disease progression.[18] The Spanish guidelines cite such evidence to justify their stance of initiating DMARD therapy as soon as, or possibly before, the diagnosis of RA is confirmed.[13 17–20]

Evidence also exists for the efficacy of all the currently available TNF inhibitors early in the course of RA.[21] The Early Rheumatoid Arthritis (ERA) trial showed that etanercept monotherapy was superior to methotrexate in reducing subsequent radiographic erosions over 2 years in patients with early erosive RA; at 24 months the American College of Rheumatology 20% (ACR20) response in the etanercept group was significantly higher than that for the methotrexate group (72% vs 59%, respectively, $p = 0.005$)[22] A subanalysis of patients with early RA in the Anti-TNF Therapy in RA with Concomitant Therapy (ATTRACT) study showed that early initiation of infliximab in combination with methotrexate provided significant reductions in radiological progression over 2 years compared with methotrexate alone.[23] Finally, the PREMIER study demonstrated that combination adalimumab plus methotrexate was more effective than either

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Table 1 Summary of the recommendations from the guidance for the use of tumour necrosis factor (TNF) inhibitors in rheumatoid arthritis (RA) in selected European countries

	Disease activity level required for initiation	Trial of DMARD	Choice of agent	Switch between agents	Treatment response measures	Time to see response	Alter frequency/dose	Radiographic monitoring	MTX combination recommended
Belgium[5] Société Royale Belge de Rhumatologie	Not specified	Two (one = MTX) for 6 months total	Any	Yes	SJC, HAQ	3–6 months	Not specified	Not mentioned	For IFX: yes Not specified for Ada or Et
Czech Republic[6] Czech Society for Rheumatology, 2007	DAS28>5.1	Two (one = MTX) for 6 months each	Any	Yes	DAS28	12 weeks	Yes	*x* Ray every 6–12 months	Yes
Denmark[7] Dansk Reumatologisk Selskab, 2000	Persistent synovitis ⩾6 joints	Two (one = MTX) for 4 months each	Not specified (Ada not included)	Not specified	SJC, TJC, pain scale, patient and physician global assessments, HAQ	4 months	Not specified	*x* Ray every 6 months for at least first 2 years, then every 2 years	For IFX: yes Not specified for Et
France[8 9] Société Française de Rhumatologie, 2007	DAS28>5.1 or DAS28>3.2 in presence of corticosteroid	One for 3 months	Any	Yes	EULAR (DAS28)	12 weeks	Yes	*x* Rays annually (or more if RA present for long time)	Yes
Haute Autorité de Santé, 2007	Radiographic progression	Anti-TNF+MTX in severe early RA (such as early joint damage)							
Germany[10] Deutschen Gesellschaft für Rheumatologie, 2006	Not specified	Two (one = MTX) for 6 months total (less if marked disease progression)	Not specified	Not specified	Not specified	3 months	Not specified	*x* Rays at least annually	Not specified
Italy[11] Società Italiana di Reumatologia, 2006	DAS>3.7 or DAS28>5.1	One for 3 months	Not specified	Yes	EULAR (DAS)	12 weeks	Not specified	Not mentioned	Yes
Romania[12] Ministry for Health, 2007	DAS28>5.1	Two (one = MTX) for 12 weeks each	Not specified	Yes	SJC, TJC, morning stiffness, ESR, CRP, DAS28	3 months	Yes for IFX	Not mentioned	Not specified
Spain[13] Sociedad Española de Reumatología, 2006	DAS28>3.2 (or lower in some circumstances)	Usually one for 3 months but none in aggressive disease	Any	Yes	DAS28, ESR, global evaluation of the disease by the patient	4 months	Yes	Annual *x* ray (plus quantitative analysis)	Yes
Sweden[14] Svensk Reumatologisk Förening, 2004	DAS28>3.2	Two for 2–3 months each or one (MTX) if rapid progression	Not specified	Not specified	Defined on individual basis?	2–3 months	Not specified	*x* Ray frequency not specified	Yes
UK[15] British Society for Rheumatology, 2004	DAS28>5.1	Two (one = MTX) for 6 months each	Any	BSR yes, NICE no (not permitted for failure to response but permitted for toxicity)	DAS28	3 months	Possible, but not generally recommended	Not mentioned	Yes

Ada, adalimumab; BSR, British Society for Rheumatology; CRP, C-reactive protein; DAS(28), (28-joint) Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; Et, etanercept; EULAR, European League Against Rheumatism; HAQ, Health assessment questionnaire; IFX, infliximab; MTX, methotrexate; NICE, National Institute for Clinical Excellence; SJC, swollen joint count; TJC, tender joint count.

agent as monotherapy in patients with early, aggressive RA.[24]

By comparing therapeutic strategies in patients newly diagnosed with RA, the BeSt study showed that initial combination therapy with methotrexate plus a TNF inhibitor provided earlier functional improvement and less progression of radiographic joint damage than either sequential monotherapy or step-up combination therapy (conventional DMARDs).[25] There is also evidence, from the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study, that in patients who initially receive and fail DMARDs other than methotrexate, combination etanercept and methotrexate is more effective than either agent alone.[26] Furthermore, no increase in toxicity was associated with combination treatment with etanercept plus methotrexate.[26]

Disease activity

Across Europe the goals of RA treatment with TNF inhibitors vary considerably. While a reduction in disease activity is a common theme, the levels of activity designated for initiation and/or cessation of TNF inhibitors differ.

When specified, a Disease Activity Score using 28 joint counts (DAS28) of over 5.1 is commonly used to define highly active disease that could qualify for TNF inhibition. The BSR guidelines for the prescribing of TNF inhibitors in the UK require two DAS measurements at least 1 month apart to confirm the ongoing activity of disease.[15] In Romania the patient must also have five or more joints with active synovitis (tender and swollen joints) plus two of the following three criteria: morning stiffness for over 60 min; erythrocyte sedimentation rate (ESR) >28 mm/h; C-reactive protein (CRP) >20 mg/litre (quantitative determination).[12] However, in Spain and Sweden moderate disease activity also qualifies for the consideration of TNF inhibitors, defined as DAS28 >3.2.[13 14] In Spain, patients who in spite of achieving remission or low DAS28 show radiographic progression or persistent inflammation in joints of special functional value, may also be considered for TNF inhibitors.[13]

In order for treatment with TNF inhibitors to continue unaltered, guidelines generally require a European League Against Rheumatism (EULAR) response to be demonstrated. EULAR response is defined as DAS28 <3.2 or DAS28 <5.1 and a decrease in DAS28 by at least 1.2 points. Denmark requires that a satisfactory response is achieved, although it is not clearly specified what this implies.[7] In Spain, in keeping with their aggressive treatment strategy, treatment should be altered if a of DAS28 <3.2 is not achieved, however, if even this is not possible, a maximum of 5 swollen and painful joints among 66 and 68 joints, respectively, should be the aim of treatment.[13]

CONCLUSIONS

It is clear that there is obvious variability in the framework for initiation of TNF inhibitors across Europe. The clinical evidence base available to the national rheumatological societies concerned is largely the same, although obviously expanding as time progresses. Therefore it is interesting that despite many similarities, there are differences in the criteria for initiation.

It is also apparent that a number of areas are not covered by the guidelines. For example, initial DMARD therapy is a requirement of all the European guidelines, and all state inadequate response as a criterion for changing to anti-TNF therapy. However, guidelines do not provide a clear definition of inadequate response to DMARDs. Such definitions are essential to ensure treatment progresses in a way that provides optimal outcomes for the patient.

Even with the similarities between guidelines, such as they are, TNF inhibitor prescribing patterns vary greatly between countries; it would seem that the prospects for people diagnosed with RA are substantially influenced by geographical location, possibly due to the different methods of funding healthcare provision. Other factors may give rise to such differences in treatment, such as levels of recognition of guidelines, the presence or absence of specialised rheumatological clinics, including early RA clinics, and familiarity with TNF inhibitors.

It should be possible for patients to be certain that they are receiving the best advice regarding their treatment, based on clinical evidence and experience, rather than the financial situation, or other influencing factors, in their respective healthcare organisation. In order to achieve this we propose that European guidance, based upon a thorough evidence review, should be prepared and made universally available in order to promote more consistent access to effective therapy.

Acknowledgements: Synergy provided writing assistance.

Funding: Wyeth provided an unrestricted grant for research and writing of this article.

Competing interests: RVV has received consulting honoraria and speaker's fees from Wyeth. EC has served on advisory boards and speaker bureaus for Abbott, Schering Plough, Wyeth, UCB Celltech and Roche. WG has served on an advisory board and Speaker Bureaus for Abbott, Schering Plough, Wyeth, UCB Celltech and Roche. SS has served in advisory boards for Abbott, Schering-Plough, Genentech and Wyeth. BC has served as a speaker and/or consultant and/or investigator for Abbott, BMS, GSK, MSD, Roche, Schering, UCB and Wyeth. PE has provided expert advice and undertaken clinical trials for Abbott, BMS, GSK, MSD, Roche, Schering, UCB and Wyeth.

Accepted 11 January 2009

Ann Rheum Dis 2009;**68**:456–459.
doi:10.1136/ard.2008.100362

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Corrections

The department of one of the authors who co-authored all of the below papers has found that the affiliations were not correct. The correct affiliations for Professor P Emery, for all of the below articles, are: [1]Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds; [2]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds, UK.

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Ann Rheum Dis 2011;**70**:1519. doi:10.1136/annrheumdis-2011-70-08

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Ann Rheum Dis 2009 68: 456-459
doi: 10.1136/ard.2008.100362