

Concordance with the British Society of Rheumatology (BSR) 2010 recommendations on eligibility criteria for the first biologic agent

Michela Frendo, John Paul Caruana Galizia, Andrew A Borg

Abstract

Aims: The aim of this study is to assess concordance with the British Society of Rheumatology (BSR) 2010 recommendations on the use of biologic therapy in Rheumatoid Arthritis (RA). The Disease Activity Score in 28 joints (DAS 28), a composite numerical score is included in these recommendations to assess disease activity and response to treatment.

Methods: Clinical notes of fifty patients who were commenced on biologic treatment between March 2010 and June 2011 were reviewed for documentation of DAS 28 scores at baseline, after approximately 6 months of commencement of treatment and at approximately 6 monthly intervals during treatment.

Results: Twenty two patients were eligible for this audit. Of these patients only half had a DAS 28 score performed prior to starting treatment, four patients had the score performed within 3-9 months of commencement of therapy and only 2 patients had continuous scores performed at six monthly intervals during treatment.

Conclusions: This audit shows that we are not adhering to the BSR recommendations. In order to improve our adherence we plan to train all staff in contact with patients on biologic treatment to perform DAS 28 scores and have a DAS 28 calculator readily available at out patients. A proforma is being developed for patients on biologic therapy to ensure that DAS 28 scores are performed at baseline and during treatment.

Michela Frendo MD MRCP*

Department of Medicine, Mater Dei Hospital, Msida, Malta
michelafrendo@hotmail.com
54, Triq Michelangelo Cagiano, St. Julians

John Paul Caruana Galizia MD MRCP

Department of Medicine, Mater Dei Hospital, Msida, Malta

Andrew A Borg DM FRCP

Dept of Medicine, Mater Dei Hospital, Msida, Malta

*corresponding author

Key Words

British Society of Rheumatology (BSR),
Disease Activity Score in twenty eight joints (DAS 28),
Disease Modifying Anti-Rheumatic Drugs (DMARDs),
Rheumatoid Arthritis (RA)

Introduction

Rheumatoid arthritis (RA), a systemic disease, is characterized by a chronic inflammatory reaction in the synovium of joints and is associated with degeneration of cartilage and erosion of juxta-articular bone. Many pro-inflammatory cytokines including tumour necrosis factor-alpha, chemokines, and growth factors are expressed in diseased joints.¹ Extra-articular features and systemic symptoms can also commonly occur.

RA has a worldwide distribution and an estimated prevalence of 1-2%. For many years non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) such as methotrexate, sulphasalazine, leflunomide and hydroxychloroquine have been used singly or in combination to manage the disease. DMARD treatment has undergone dramatic changes over the past decade and biologic DMARD therapy has revolutionized the management of the disease.² The development of biologic DMARDs followed an increased understanding in the pathogenesis of inflammatory arthritis with the identification of cytokines which are key players in the inflammatory process. Their target is highly specific with the mode of action easier to elucidate than with traditional DMARDs.

Biologic drugs have allowed rheumatologists to satisfactorily control RA resistant to conventional DMARDs. All the biologic DMARDs are very expensive and their unrestricted use would be unaffordable.³ Thus judicious use and review of such treatment is imperative to identify partial or non responders.

The BSR working party on biologic therapies started to work on guidelines to produce recommendations on the appropriate use of these therapies in RA in 2007. The three recommendations which were finalized and published in March 2010 are used in this audit.⁴ They include eligibility criteria for biologic treatment and continuous monitoring of response to treatment using a validated score, the Disease Activity Score of 28 joints (DAS 28).

DAS 28 is a composite, numerical score combining several discrete measures of RA activity into a single grading of disease severity. It comprises objective (ESR), subjective (patient well being) and semi-objective (joint swelling and joint tenderness) criteria in 28 joints (including shoulder, elbow, wrist, metacarpophalangeal and proximal interphalangeal and knees) commonly involved in RA (Table 1).

Table 1: How to calculate DAS28

Variables	Result
Number of swollen (0-28)	
Number of tender joints (0-28)	
ESR (or CRP)	
Visual analogue scale (VAS) disease activity (0-100mm)	

How to calculate the DAS 28 score

1. Collect the data for the number of swollen and the number of tender joints, the ESR (or CRP) and the VAS for disease activity.
2. Use the equation below

$$\text{DAS28} = 0.56 * \sqrt{(\text{TENDER JOINTS}) + 0.28 * \sqrt{(\text{SWOLLEN JOINTS}) + 0.70 * \ln(\text{ESR/CRP}) + 0.014 * \text{VAS}}}$$

It is used to assess disease activity and monitor response to treatment with DMARDs. The European League Against Rheumatism (EULAR), published response criteria suggesting that biologics should be stopped if there is less than 20% improvement in DAS 28 at 3-6 months.⁵ These response criteria were utilized by the BSR in the recommendations.

The above guidelines were chosen because they are recent, evidence based and comprehensive. If we are not adhering to the above recommendations we propose to implement change in our department to be consistent and give to our patients evidence based care.

The primary aim of this audit was to assess concordance of departmental management with BSR 2010 recommendations on biologic therapy use in RA. Secondary aims were auditing of the use of the DAS 28 prior to starting biologic therapy and its use to measure the response to treatment with biologic agents.

Patients and Methods

Patients

The demographic data of all patients with RA commenced on an anti-TNF agent and recorded in the database of the pharmacy department at Mater Dei Hospital from March 2010 to June 2011 were collected. The records held by the specialist nurse on patients receiving biologic therapy were also reviewed to ascertain completeness of recruitment of all the patients.

Methods

This is a retrospective audit. The case notes of the patients were reviewed to extract the following information:

1. DAS 28 score recorded at baseline (before starting treatment with anti TNF therapy).
2. Whether the DAS 28 score at baseline was appropriate for commencement of biologic therapy (i.e. ≥ 3.2).
3. Use of non biologic DMARD prior to starting anti -TNF.
4. DAS 28 scores recorded after commencement of treatment.

5. Achievement of an adequate EULAR response after 3 to 9 months of starting anti-TNF ($\geq 20\%$ improvement in DAS 28)
6. Regular recording of DAS 28 scores during treatment.

Statistics

Non parametric statistics were used throughout the analysis

Results

Fifty patients were commenced on biologics from March 2010 to June 2011 (16 months). Of these patients, 28 (56%) suffered from RA, diagnosed according to the 1987 American College of Rheumatology Criteria. These latter patients were included in the study. Twenty two (44%) patients were excluded from the study. These included those patients who were treated with biologic treatment for conditions other than RA such as Ankylosing Spondylitis, Psoriatic Arthritis and Juvenile Idiopathic Arthritis and those patients who had incomplete data recorded in the hospital notes because the patients were also visiting their rheumatologist in clinics outside the hospital.

Four patients did not start treatment, despite having a biologic treatment prescribed. These were patients who after appropriate counselling about potential side effects of anti-TNF therapy refused the treatment.

Two further patients were excluded from the study because they were already on biologic treatment prior to settling in Malta.

This left us with 22 patients eligible for the audit.

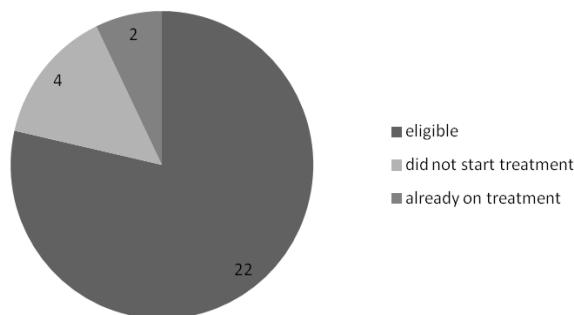


Figure 1: Number of patients who suffered from RA and were enrolled in the study

Recommendation 1

Biologic therapies are recommended as options for treatment of adults with the following characteristics:

- A. Active RA as measured by DAS 28 ≥ 3.2
- B. Have undergone trial of two DMARDs including methotrexate (unless contraindicated). A trial being defined as at least two DMARDs usually given concurrently over a 6 month period with 2 months at standard doses

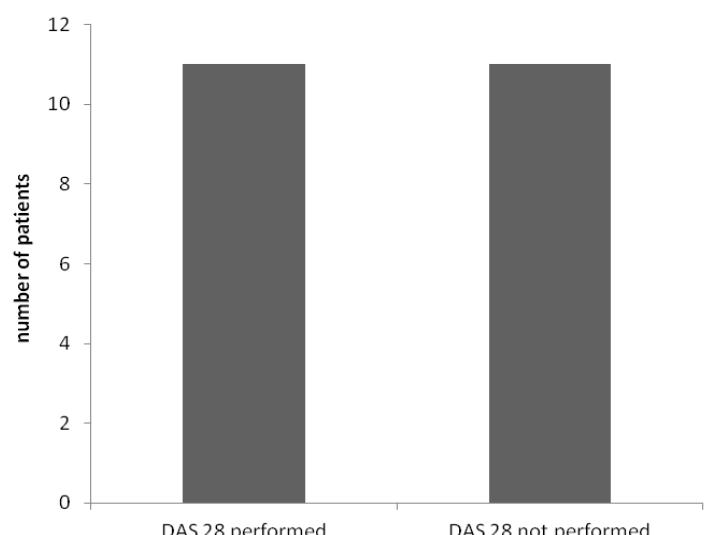


Figure 2: Number of patients who had DAS 28 performed before starting treatment

Results:

Of the 22 patients included in the audit, 11 patients had a DAS 28 performed prior to starting biologic therapy.

All 11 patients had DAS scores >3.2 .

Initial control of disease activity with at least two DMARDs at standard doses was seen in 91% of patients.

Recommendation 2

Treatment should be continued if there is an adequate response to treatment following the first 6 months of continuous treatment. An adequate response is defined as a good or moderate EULAR response.

Results:

Four patients had a DAS 28 score performed within 3 to 9 months of starting treatment. Of these 4 patients only 2 patients had a DAS 28 performed before starting treatment. Thus the EULAR response criteria could only be measured in the latter 2 patients. Both patients had a moderate EULAR response (Figure 3).

		DAS-28		
Change in DAS-28	>5.1	≤ 5.1 and >3.2	≤3.2	
>1.2	Moderate	Moderate	Good	
>0.6 and ≤1.2	None	Moderate	Moderate	
≤ 0.6	None	None	None	

Figure 3 - The EULAR response criteria⁵

Recommendation 3

After initial response, anti TNF treatment in RA should be monitored with assessment of DAS 28 no less frequently than 6 monthly. Anti TNF therapy should be withdrawn if an inadequate response is seen despite 6 months of continuous therapy

Results:

Of the 22 patients suffering from RA who were started on biologic agents only 2 patients had continuous monitoring as recommended (Figure 4).

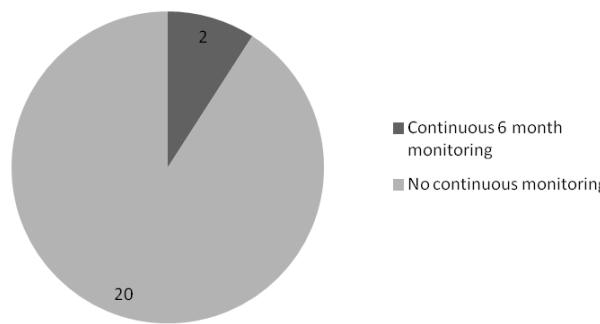


Figure 4: Number of patients who had continuous DAS 28 monitoring during treatment

Discussion

Biologic drugs represent an exciting advance in the treatment of RA. The response to biologics is not uniform or universal. Generally 20% of patients experience a 60% improvement in DAS28 while 60% of patients will experience a 20% improvement in the same score. Some patients fail to respond altogether and early recognition of these patients is important as these drugs are very expensive (approximately 10,000 euro per patient per year) and have potentially serious side effects particularly infection. Treatment of patients who respond to treatment is long term so the cost is ongoing. These drugs are an important resource which has to be used appropriately, judiciously and effectively.

Use of the DAS 28 to commence, change or stop biologic therapies in RA is to a degree controversial. While we have no better gold standard at present, there is concern that DAS 28 fails to measure metatarsophalangeal

joint involvement given that these joints are commonly involved in the disease process. Also, the subjective criterion (patient well-being) and joint tenderness (by perhaps applying firmer pressure to the joints) can greatly skew the result obtained. Therefore intra- and inter-reliability of measurement can be significant.

In contrast to the BSRBG recommendations on eligibility criteria for first biologic which include a DAS 28 score ≥3.2, the National Institute of Health and Clinical Excellence (NICE) have an entry level for biologic therapy in RA of 5.1. The BSRBG suggest that this is an arbitrary level which is driven by economics rather than purely patient needs. The group argues that a patient with a DAS28 of, for example, 4.8, is just as likely to have disease progression but would not be eligible for biologic therapy.

It is clear from this audit that we are not adhering to the above recommendations in our Department.

Some reasons for this include:

1. DAS 28 calculator not readily available at out-patients;
2. The high turnover of staff in the department - doctors working in the department for only a few months are not adequately trained to perform DAS 28 scores.
3. Few of the permanent staff have had formal training in DAS 28 measurement techniques to reduce intra- and inter- observer variability.
4. Time constraints including difficulty in scheduling appointments in line with recommendations (at least 6 monthly intervals). Current first available follow up appointments for most of the consultants is greater than 6 months.

Recommendations following audit

1. A proforma is being developed to ensure that all RA patients have a baseline DAS score and prior non biologic DMARD history recorded prior to commencement of biologic therapies.
2. Plans are in hand for a biologic clinic to be set up to allow better scheduling of appointments for patients on biologics and improve detection of potential adverse reactions. This will complement the imminent commencement of an early arthritis clinic for detection of persistent inflammatory arthritis.
3. Training of all staff in the Department caring for patients on biologics to standardize performance of the DAS 28 and consequently minimize inter- and intra- observer variation.
4. Regular review of patients on biologic therapies to identify patients who have an inadequate response to biologics according to BSR and EULAR criteria. In these patients switching of a

biologic or withdrawal of biologic would lead to more effective and efficient use of resources.

Acknowledgments

The authors thank Dr. F Camilleri Vassallo, Dr. B Coleiro and Dr. PJ Cassar for their consent to study their patients. Thanks also to Mrs. D Aquilina and Mrs. L Grech for allowing access to their respective biologic database.

References

1. Feldmann M, Maini R.N. Anti – TNF therapy of rheumatoid arthritis: What have we learned? *Annu Rev Immunol* 2001;19:163-196.
2. Smolen JS, Aletaha D, Koeller M, Wiesman MH, Emery P. New therapies for treatment of rheumatoid arthritis. *Lancet* 2007;370:1861–74.
3. Finckh A, Bansback N et al. Treatment of Very Early Rheumatoid Arthritis With Symptomatic Therapy, Disease-Modifying Antirheumatic Drugs, or Biologic Agents: A Cost-Effectiveness Analysis. *Ann Intern Med* 2009;151:612-621.
4. Deighton C, Hyrich K, Ding T, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. *Rheumatol (Oxford)* 2010;49:1197-9.
5. Fransen J, van Riel PL The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol*. 2005 Sep-Oct;23(5 Suppl 39)S93-99.