Major Cost Savings Associated with Biologic Dose Reduction in Patients with Inflammatory Arthritis

Abstract:

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Abstract

The purpose of this study was to explore whether patients with Inflammatory Arthritis (IA) (Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) or Ankylosing Spondylitis (AS)) would remain in remission following a reduction in biologic dosing frequency and to calculate the cost savings associated with dose reduction. This prospective non-blinded non-randomised study commenced in 2010. Patients with Inflammatory Arthritis being treated with a biologic agent were screened for disease activity. A cohort of those in remission according to standardized disease activity indices (DAS28<2.6, BASDAI<4) was offered a reduction in dosing frequency of two commonly used biologic therapies (etanercept 50mg once per fortnight instead of weekly, adalimumab 40mg once per month instead of fortnightly). Patients were assessed for disease activity at 3, 6, 12, 18 and 24 months following reduction in dosing frequency. Cost saving was calculated. 79 patients with inflammatory arthritis in remission were recruited. 57% had rheumatoid arthritis (n=45), 13% psoriatic arthritis (n=10) and 30% ankylosing spondylitis (n=24). 57% (n=45) were taking etanercept and 43% (n=34) adalimumab. The percentage of patients in remission at 24 months was 56% (n=44). This resulted in an actual saving to the state of approximately 600,000 euro over two years. This study demonstrates the reduction in biologic dosing frequency is feasible in Inflammatory Arthritis. There was a considerable cost saving at two years. The potential for major cost savings in biologic usage should be pursued further.

Introduction

Biologic agents have revolutionised the management of patients with inflammatory arthritis, particularly rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). They have been proven to greatly improve disease activity, reduce or prevent joint damage and help patients to continue in employment. The drugs are extremely expensive. The annual spend worldwide on Tumour Necrosis Factor (TNF) inhibitors in RA has been estimated at 18 billion euro. In Ireland, the cost of treating one patient per year at the licensed dosage with the most commonly used agents etanercept or adalimumab is approximately 13,500 euro. The state bears this cost except for those on the Drug Payments Scheme who currently contribute a maximum of 1728 euro per annum. With a population of 4.6 million the cost in the Republic of Ireland is approximately 130 million euro annually. It is clear therefore that any sustained reduction in biologic dose or dosing frequency could lead to major cost savings. Other potential advantages of reduced dosing include reduced side-effects such as infections and possibly demyelinating disease. Reducing either the dose or the dosing frequency of biologic agent in those whose inflammatory arthritis is in remission or with low disease activity (LDA) has been shown to be feasible in a number of small studies[2-9]. The aim of this study was to reduce the dosing frequency of biologic agents in those whose inflammatory arthritis was in remission and to calculate the associated cost savings at two years.

Methods

This prospective single-centre, observational, non-blinded non-randomised study commenced in 2010. Patients with inflammatory arthritis including seropositive or seronegative rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis attending the biologic clinic at our hospital were screened for disease activity. A cohort of those in remission on Etanercept or Adalimumab (defined as Disease Activity Score (DAS) 28 <2.6 or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) <4) for at least six months prior to study entry was offered a reduction in biologic dosing frequency - etanercept 50mg once per fortnight instead of weekly or adalimumab 40mg once per month instead of fortnightly.

After obtaining consent, those willing to participate were assessed for disease activity at 3, 6, 12, 18 and 24 months following the reduction in dosing frequency. During the two year period of observation patients with a single flare of disease activity were permitted to remain on the reduced dosing frequency. The flare was treated with one intramuscular injection of MethylPrednisolone 120mg. If there was a further flare the frequency of biologic administration reverted to the licensed frequency. Those with a single flare but whose inflammatory arthritis was in remission at two years were considered to have remained in remission. Demographic data including gender, age, disease duration, duration of biologic agent, disease type, biologic administered, concomitant methotrexate and concomitant NSAID use were collected. DAS28 and health assessment questionnaire (HAQ) was calculated for patients with seropositive rheumatoid arthritis, seronegative rheumatoid arthritis and psoriatic arthritis. BASDAI and BASFI (Bath Ankylosing Spondylitis Functional Index) were calculated in patients with Ankylosing Spondylitis.

Cost saving was calculated as the difference in cost between the actual amount of biologic agent used compared with the cost if the licensed dosage had been used for two years. Statistical analysis was performed using SPSSv20 for windows. Descriptive statistics were used for demographic data. Paired sample T test was used to compare DAS28, HAQ, BASDAI and BASFI scores at 0, 3, 6, 12, 18 and 24 months. The primary outcome was the percentage of patients who remained in remission at two years following a reduction in biologic dosing frequency.

Results

Seventy nine patients were recruited. All patients had inflammatory arthritis and had been in remission for a minimum of 6 months prior to recruitment. Demographic data is shown in Table 1. Mean age was 49.5 years. Mean duration of inflammatory arthritis was 7 years. (Range 1-40). Fifty seven per cent (n=45) had a diagnosis of rheumatoid arthritis, of whom 78% were seropositive and 22% seronegative. Thirteen percent had psoriatic arthritis (n=10) and 30% ankylosing spondylitis (n=24) (Figure 1). Fifty seven percent (n=45) were taking etanercept and 43% (n=34) adalimumab.

Mean duration of anti-TNF therapy prior to dose reduction was 31 months (range 12-72). Forty one per cent (n=33) were on biologic monotherapy. Fifty three per cent (n=42) were taking concomitant methotrexate while 6% (n=4) were taking an alternative DMARD including salazopyrin or leflunomide. Using paired sample t-tests in SPSSv20, in those who stayed in remission, no significant difference in DAS28, HAQ or BASDAI scores from baseline to 24 months was identified ($p<0.05$). The percentage overall of those in remission fell over two years of follow up from 83% (n=66) at 3 months, to 75% (n=59) at 6 months, 61% (n=48) at 1 year and 56% (n=44) at 2 years (Figure 2).

Discussion

This study provides further evidence that biologic dose reduction is feasible in Rheumatoid arthritis, Psoriatic arthritis and Ankylosing Spondylitis. A number of studies, both prospective and observational, have in recent years shown significant proportions of patients remaining in remission between 1 and 2 years after dose reduction[2-9]. The studies have in general used the two most commonly prescribed sub cutaneous biologic agents, Etanercept and Adalimumab.[1,3-8] They include relatively small numbers of patients but consistently show a pattern of remission

maintenance. The rate of remission maintenance varies with the type of inflammatory arthritis, and in general appears lower in rheumatoid arthritis. In Ankylosing Spondylitis approximately 70 to 80 percent appear to remain in remission, with figures of 60 to 70% in Psoriatic Arthritis and 30 to 40% in Rheumatoid Arthritis. In our study the percentage overall of those with Inflammatory Arthritis maintaining remission fell from 83% at 3 months to 56% at 2 years. Only one other study has a two year follow up and it is clearly possible that the percentage maintaining remission would fall further with time.

In Rheumatoid arthritis the percentage of patients achieving remission with standard licensed doses of biologic agents is relatively low at 30 to 40%[1]. As a result, some studies focus on the attainment and maintenance of low disease activity (LDA) where patients show substantial reduction in disease activity without achieving remission. Maintenance of low disease activity following biologic dose reduction has been demonstrated in a prospective, randomized trial, the PRESERVE study[2]. In this large trial involving 834 patients, 80% of those initially achieving LDA with standard dose Etanercept for 6 months maintained LDA despite reducing the dose of the drug by 50% for a further year. The percentage maintaining LDA was not significantly different compared with the group that remained on the standard dose of Etanercept for the full 18 months. It may therefore be possible to dose reduce in those with substantial clinical benefit but not remission, without loss of benefit. The question of possible differences in radiographic joint damage between standard and lower dose biologic agent in RA has shown conflicting results. Tada et al found higher rates of joint damage in those on lower dose Etanercept despite similar responses in terms of clinical benefit[3]. However Raffeiner et al showed identical capability to arrest radiographic joint damage with standard and reduced doses of Etanercept[4].

Our study has a number of limitations. The sample size is small and includes patients with 3 types of inflammatory arthropathy. There was no control group in which biologic doses were not reduced. We chose to maintain those with one flare of Inflammatory Arthritis on the reduced dosing frequency where a single dose of MethylPrednisolone 120mg settled the flare. This was a 'real world' decision as it would have seemed excessive to effectively double patients' biologic dose back to the licensed dose on account of what was frequently a brief flare. While this study included Etanercept and Adalimumab, dose reduction may be possible with other anti-TNF agents and other biologic agents with different targets and mechanisms of action such as Tocilizumab, Abatacept and Rituximab. While the advent of biosimilars should reduce biologic cost by 20-30 percent, the cost of dose reduction offers the potential for savings of at least a similar magnitude[5]. The cost implications of successful dose reduction are considerable. Major cost savings have already been shown in dose reduction studies.[4,6,7] The dose frequency reduction in our study resulted in an actual saving in a small cohort of 600,000 euro at 2 years. The estimated annual cost of sub cutaneous biologic agents for Inflammatory Arthritis in the Republic of Ireland is approximately 130 million euro. At an average cost of 13,500 euro per patient per annum this suggests there are c.10,000 patients with IA on these agents. It is known that in excess of 50% of those with Ankylosing Spondylitis or Psoriatic Arthritis can achieve remission with standard dose biologics while up to 70% of patients with RA achieve remission or Low Disease Activity on standard doses. If it was possible for example to successfully dose reduce 25% of those with Inflammatory Arthritis on biologic agents the savings could amount to tens of millions of euro at one year.

This study suggests reduction in biologic dosing frequency is feasible in inflammatory arthritis. It resulted in considerable cost saving at two years. A substantial proportion of patients (56%) remained in remission at two years. A reduction in biologic dosing frequency should be considered in patients with Inflammatory Arthritis in remission or with low disease activity in Rheumatoid Arthritis.

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