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Original article

Information on glucocorticoid therapy in the main studies of biological agents

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ABSTRACT

Objective: To evaluate reported information on prednisone therapy in the main studies of biological agents used to treat rheumatoid arthritis (RA).
Methods: We reviewed 66 publications (including four abstracts), including 11 studies of infliximab, 19 of etanercept, eight of adalimumab, five of golimumab, four of certolizumab, four of rituximab, eight of abatacept, and seven of tocilizumab.
Results: Whether concomitant prednisone therapy was used, it was specified in only 56 (85%) of the 66 publications. Only 42 (64%) publications indicated that the prednisone dosage remained unchanged throughout the study. The maximum prednisone dosage allowed was specified in only 39 (59%) reports and was lower than 8 mg/day in only four (6%) studies. Data enabling determination of the mean daily prednisone dosage in prednisone-treated patients was available for only eight (12%) studies; the mean dosage ranged from 5.0 to 9 mg/day (mean, 7.1 ± 1.5). The percentage of patients receiving prednisone therapy was reported for only 41 (62%) studies. All the above-mentioned information was available in only two (3%) study reports. The percentage of patients on prednisone therapy ranged from 34% to 93% (mean, 58 ± 13%) overall and varied across biological agents as follows: abatacept, 74.4%; golimumab, 67.9%; infliximab, 60.6%; certolizumab, 57.5%; rituximab, 57.5%; etanercept, 54.4%; tocilizumab, 52.8%; and adalimumab, 50.4%. These percentages did not decline between 1997 and 2010.
Conclusion: Study reports provide inadequate information on prednisone therapy during biological treatment for RA.

1. Introduction

In studies of biological agents used to treat rheumatoid arthritis (RA), the multivariate analyses suggest a prominent role for continued glucocorticoid therapy in the occurrence of some of the infectious complications [1]. In a study based on the CORRONA registry, the excess risk of infection related to prednisone monotherapy in dosages lower than 10 mg/day was 30% [2]. Similar results were obtained in a recent meta-analysis of the 15 best retrospective studies on infections in RA patients taking low-dose prednisone therapy [3].

The most accurate method of evaluating the excess risk of infection related to the concomitant use of biological agents and prednisone would be to perform prospective randomized studies comparing prednisone alone, biological therapy alone, and both in combination. It is now highly unlikely that such studies will be performed in patients with established RA. Randomized studies would provide quantitative information on the advantages associated with low-dose prednisone therapy taken concomitantly with biological therapy. Low-dose glucocorticoid therapy, similar to methotrexate therapy, cannot prevent the progression of early arthritis to RA [4]. Nevertheless, low-dose glucocorticoid therapy adds to the symptomatic relief provided by biological therapy and may contribute to slow joint damage progression, albeit to a considerably smaller degree [5]. A 2007 Cochrane review of 15 studies in 1414 patients showed that low-dose prednisone therapy was associated with a slower pace of disease progression in 14 of 15 studies [6]. A systematic literature review by European experts produced similar results [7]. In the BeSt trial of four treatment strategies for early RA, radiographic disease progression was 1.0 point on the total modified Sharp score with three disease-modifying antirheumatic drugs (DMARDs) and 7.5 mg/day prednisone, compared to 0.5 point with methotrexate plus infliximab and 2.0 points with methotrexate alone; in the first two groups, the clinical effects were not significantly different [8].

Dependency on a drug does not always indicate efficacy. Nevertheless, the high rate of continued prednisone therapy in patients started on biological therapy suggests that part of the benefits obtained with the DMARD-biotherapy-prednisone combination may be ascribable to prednisone. In a study of 110 patients started

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on TNFα antagonist therapy, including 72% on low-dose prednisone at baseline, 61% were still on low-dose prednisone after 1 year and the mean prednisone dosage over the first treatment year was only 28% lower (about 3 mg/day) than the mean prednisone dosage during the preceding year [9]. In two randomized placebo-controlled trials of prednisone withdrawal, documented RA flares were common, even among patients initially on very low prednisone dosages (1–4 mg/day) [10,11].

The use of low-dose prednisone may be a marker for severe disease. Therefore, studies of the safety and efficacy of biological agents should take the use of prednisone into account; however, many did not [12]. Additional reasons for obtaining information on concomitant prednisone therapy include the possibility that the beneficial and detrimental additive effects of prednisone and biotherapy vary across biological agents. Furthermore, the proportion of patients on prednisone and the daily prednisone dosage probably vary across studies.

Here, our objective was to review information on prednisone therapy in patients enrolled in studies of biological agents. We reviewed the reports of the main studies on the efficacy of biological agents in patients with RA.

2. Methods

We listed the main DMARD- or placebo-controlled studies of biological agents in patients with RA (Table 1) (references in the appendix in the online supplement to this article). We then listed the items to be extracted from each article: year of publication; number of treated patients; whether prednisone use was reported in the methods and/or results sections; whether the maximum prednisone dosage allowed was specified and, if so, the value; whether the percentage of patients on prednisone was specified and, if so, the value; the mean prednisone dosage in patients on prednisone (reported or computed if possible based on the available data); and whether the prednisone dosage was left unchanged throughout the study. These data were entered into an Excel spreadsheet then transferred to SPSS-12.0. None of the studies involved separate assessments of the efficacy and safety of biological agents in patients with and without prednisone therapy.

3. Results

We identified 66 publications (listed in the Appendix A) including 62 original articles and four abstracts presented at meetings. Among them, 11 reported studies on infliximab (including one abstract), 19 on etanercept (including two abstracts), eight on adalimumab, five on golimumab, four on certolizumab, four on rituximab, eight on abatacept (one abstract), and seven on tocilizumab (Table 1).

Information on the use of oral prednisone was given in the methods and/or results sections of only 56 (85%) publications (55/62 articles and one abstract upon four): 10 of 11 publications on infliximab, 16 of 19 on etanercept, five of eight on adalimumab, five of five on golimumab, three of four on certolizumab, four of four on rituximab, six of eight on abatacept, and seven of seven on tocilizumab. The maximum daily prednisone dosage allowed was specified in only 43 (65%) publications: eight of 11 on infliximab, 11 of 19 on etanercept, two of eight on adalimumab, two of five on golimumab, two of four on certolizumab, four of four on rituximab, seven of eight on abatacept, and seven of seven on tocilizumab.

The maximum dosage allowed was less than 8 mg/day in only four (6%) studies (two upon 11 on infliximab, 0/19 on etanercept, 0 upon eight on adalimumab, 0 upon five on golimumab, one upon four on certolizumab, 0 upon four on rituximab, one upon eight on abatacept, and 0 upon seven on tocilizumab).

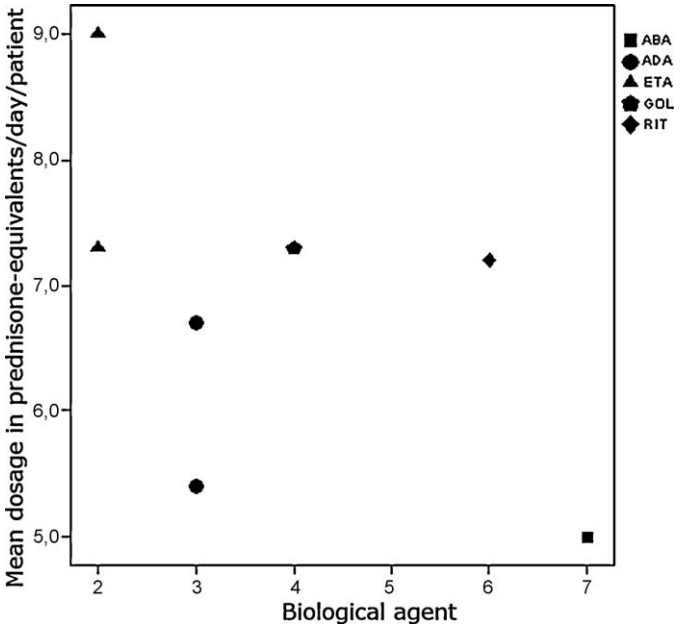

Fig. 1. Mean daily prednisone dosage in prednisone-treated patients enrolled in the eight studies for which relevant information was available. In two studies of etanercept, the mean dosage was 9 mg and the superimposition of the two triangles representing these studies explains that seven symbols are visible instead of eight. ABA: abatacept; ADA: adalimumab; ETA: etanercept; GOL: golimumab; RIT: rituximab.

The proportion of patients on glucocorticoid therapy was specified explicitly in only 41 (64%) studies: eight upon 11 (73%) on infliximab, 13/19 (74%) on etanercept, five upon eight (63%) on adalimumab, two upon five (40%) on golimumab, two upon four (50%) on certolizumab, two upon four (50%) on rituximab, five upon eight (63%) on abatacept, and four upon seven (57%) on tocilizumab. This proportion ranged from 34% to 93% (mean, 58% ± 13%) with no statistically significant differences across biological agents.

The mean daily prednisone dosage among patients on prednisone therapy was reported in eight (12%) publications: 0/11 on infliximab, three upon 19 on etanercept (references [13], [15], and [16] in the appendix), two upon eight on adalimumab (references [33] and [36] in the appendix), one upon five on golimumab (reference [43] in the appendix), 0 upon four on certolizumab, one upon four on rituximab (reference [51] in the appendix), one upon eight on abatacept (reference [55] in the appendix), and 0 upon seven on tocilizumab. The mean daily prednisone dosage ranged from 5.0 to 9 mg (mean, 7.1 ± 1.5 mg) (Fig. 1). Based on the data in three reports (1,7,48), the daily prednisone dosage may have been 10 mg or more in some patients. These high dosages do not seem to have been used in the other studies, although the information on this point is scant at times. A review report (START)[7] specified the proportions of patients taking more than 10 mg of prednisone per day in the placebo group (4.4%) and in the two infliximab arms (3.1% and 3.9%, respectively) [7]. Only 42 (64%) reports specified that the prednisone dosage remained unchanged throughout the study (nine upon 11 on infliximab, eight upon 19 on etanercept, three upon eight on adalimumab, five upon five on golimumab, two upon four on certolizumab, four upon four on rituximab, four upon eight on abatacept, and seven upon seven on tocilizumab).

Information on all the above-mentioned items was available in only two (3%) reports (0/11 on infliximab, one upon 19 on etanercept, 0 upon eight on adalimumab, 0 upon five on golimumab, 0 upon four on certolizumab, one upon four on rituximab, 0 upon eight on abatacept, and 0 upon seven on tocilizumab).