Contemporary Clinical Trials Communications 8 (2017) 49–54

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Remission induction by Raising the dose of Remicade in RA (RRRR) study: Rationale and study protocol for a randomized controlled trial comparing for sustained clinical remission after discontinuation of infliximab in patients with rheumatoid arthritis

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ARTICLE INFO

Keywords:
Rheumatoid arthritis
Infliximab
TNF-α
Randomized controlled trials
Sustained remission
Protocol paper

ABSTRACT

Infliximab, an inhibitor of TNF-α, is one of the most widely used biological disease-modifying antirheumatic drugs. Recent studies indicated that baseline serum TNF-α could be considered as a key indicator for optimal dosing of infliximab for RA treatment to achieve the clinical response and its sustained remission. The Remission induction by Raising the dose of Remicade in RA (RRRR) study is an open-label, parallel group, multicenter randomized controlled trial to compare the proportions of clinical remission based on the simplified disease activity index (SDAI) after 1 year of treatment and its sustained remission rate after another 1 year between the investigational treatment strategy (for which the dose of infliximab was chosen based on the baseline serum TNF) and the standard strategy of 3 mg/kg per 8 weeks of infliximab administration in infliximab-naïve patients with RA showing an inadequate response to MTX. The primary endpoint is the proportion of patients who kept discontinuation of infliximab 1 year after discontinued infliximab at the time of 54 weeks after the first administration of infliximab. The secondary endpoints are the proportion of clinical remission based on SDAI and changes in SDAI from baseline at each time point, other clinical parameters, quality of life measures and adverse events. Target sample size of randomized patients is 400 patients in total. The main results of the RRRR study are expected to be published at the end of 2017.

1. Introduction

Rheumatoid arthritis (RA) is a progressive systemic inflammatory disease characterized by joint destruction and functional disability [1]. RA occurs globally in about 1.0% of the general population, with 2–4-times higher prevalence in women than in men [2]. Although the etiology of RA is not quite clear, some inflammatory cytokines such as tumor necrosis factor α (TNF-α) have been shown to play a central role in the occurrence and progression of RA [3].

Infliximab, an inhibitor of TNF-α, is one of the most widely used biological disease-modifying antirheumatic drugs (DMARDs); combined use of infliximab and methotrexate (MTX) shows clinical and radiographic benefits compared with placebo in patients inadequately controlled with therapeutic doses of MTX [4]. Because the therapeutic effects of infliximab (plus MTX) have been demonstrated in several clinical studies [5–11], the primary goal of RA treatment has shifted from the achievement of clinical remission to sustained remission without biologic DMARDs particularly in patients with RA in sustained

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http://dx.doi.org/10.1016/j.conctc.2017.08.007
Received 29 January 2017; Received in revised form 7 August 2017; Accepted 15 August 2017
Available online 17 August 2017

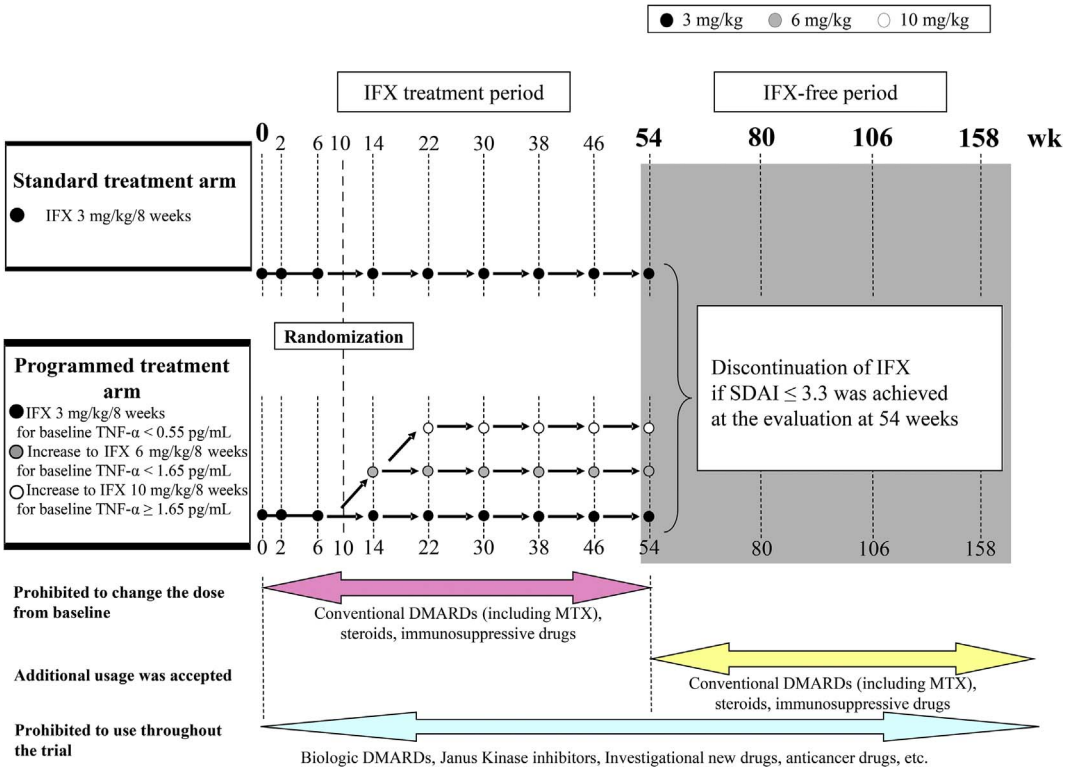

Fig. 1. Study Design of the RRRR study.

remission [12,13].

The first study reporting the possibility of biologic-free treatment in patients with RA was the TNF20 study [10]. This trial indicated that early treatment of RA with infliximab induces a permanent response that persists, even after discontinuation of the drug. After publication of the TNF20 study, the Behandelstrategieën (BeSt) study evaluated biologic-free treatment in much larger cohort [8,14]. Sixty-four percent of patients with early RA were able to discontinue infliximab and in 56% patients treated with MTX monotherapy for 2 years, low disease activity was maintained and progression of joint damage was inhibited. In established RA patients exhibiting an inadequate response to MTX, the Remission induction by Remicade in RA patients (RRR) study also examined the possibility of biologic-free remission or low disease activity [15]. The patients enrolled in the study were those who had reached and maintained a disease activity score 28 (DAS28) of less than 3.2 for more than 24 weeks with infliximab treatment and who then agreed to discontinue the treatment. Among the 102 evaluable patients who completed the study, 56 (55%) maintained low disease activity after 1 year and showed no progression in radiological damage and functional disturbance; 44 (43%) remained in clinical remission (DAS28 $<$ 2.6).

In this context, subanalysis of the dose-escalation study of infliximab with MTX (RISING study) showed a significant interaction between baseline TNF-α and the dose of infliximab in the clinical response. Additionally, the clinical response and disease activity were significantly better when the treatment was applied at 10 mg/kg than at 3 and 6 mg/kg, with a high baseline TNF-α (baseline TNF-α values: 1.65 pg/mL or greater) [16]. To achieve the clinical response and its sustained remission, serum TNF-α could be considered as a key indicator for optimal dosing of infliximab for RA treatment.

The Remission induction by Raising the dose of Remicade in RA (RRRR) study was planned to compare the proportions of clinical remission based on the simplified disease activity index (SDAI) after 1 year of treatment and its sustained remission rate after another 1 year between the investigational treatment strategy (for which the dose of infliximab was chosen based on the baseline serum TNF) and the standard strategy of 3 mg/kg per 8 weeks of infliximab administration in infliximab-naïve patients with RA showing an inadequate response to MTX. In this study, we describe the study design and baseline characteristics of the enrolled patients.

2. Methods

2.1. Eligible patients

Patients with RA were eligible for enrollment if they had active disease equal to or greater than 6 mg MTX weekly, were 18 years of age or older at the time of enrollment, and experienced no prior infliximab use. Patients were excluded if they were taking corticosteroids at doses higher than 10 mg prednisolone equivalents/day, had an SDAI $\leq$11.0, had severe infections, had active tuberculosis or evidence of latent tuberculosis, were given a diagnosis of systemic lupus erythematosus or any other form of concomitant arthritis, had congestive heart failure, or were pregnant or lactating women during or 6 months after treatment. All the patients gave written informed consent in accordance with the Declaration of Helsinki, and the trial was approved by the institutional review board at each participating institution. This trial was registered with University Hospital Medical Information Network (UMIN; number UMIN000005113).

2.2. Study design

The RRRR study was conducted as an open-label, parallel group, multicenter randomized controlled trial. Eligible patients with RA who had active disease despite taking equal to or greater than 6 mg of MTX weekly were able to participate. They were randomly assigned in a 1:1 ratio to receive either a standard treatment (standard dose of 3 mg/kg infliximab every 8 weeks) or a programmed treatment with the starting dose of infliximab based on the three categories of baseline TNF-α (low, less than 0.55 pg/mL; intermediate, 0.55 pg/mL or greater to less than 1.65 pg/mL; and high, 1.65 pg/mL or greater) in addition to baseline