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## Maintenance of Treatment with Infliximab in Ankylosing Spondylitis:

### Results of a One-Year Randomized Controlled Trial, Comparing Systematic versus On-Demand Regimen

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Running head: Infliximab maintenance in ankylosing spondylitis

## Abstract

*Objective.* Continuous treatment with the anti-tumor necrosis factor  $\alpha$  antibody infliximab is efficacious in ankylosing spondylitis (AS), whereas treatment discontinuation results in disease relapse, with variable delay. Objective of this study was to compare efficacy between continuous treatment with infliximab, and a treatment adapted to symptoms recurrence. Addition of methotrexate (MTX) to infliximab was also tested.

*Methods.* Patients with active AS were randomly assigned at week 0 to receive infliximab every 6 weeks (Q6), or upon symptoms recurrence (on-demand), following 3 infusions at weeks 4, 6, and 10. Patients in the latter group were randomly assigned to receive MTX or not. Monitoring was performed over one year. The primary end point was the proportion of patients with a 20% improvement response according to the ASsessment in AS (ASAS) criteria, at week 58.

*Results.* Of 247 patients, 124 were assigned to Q6, and 123 to on-demand regimen. Among the latter, 62 received MTX, and 61 did not. Greater proportion of patients fulfilled ASAS20 response at week 58 in Q6, than in on-demand group (75% vs 46%;  $P < 0.0001$ ). Patients in Q6 group received more infliximab infusions after week 10, than those in on-demand group (mean  $\pm$  standard deviation:  $5.8 \pm 2.2$  vs  $3.5 \pm 2$ ;  $P < 0.0001$ ). Addition of MTX did not significantly affect the proportion of patients fulfilling ASAS20 response at week 58, nor the number of infliximab infusions administered.

*Conclusion.* Continuous treatment of AS with infliximab was more efficacious than on-demand regimen, and addition of MTX to infliximab provided no significant benefit.

Ankylosing spondylitis (AS), is the prototypical form of a group of inflammatory rheumatic diseases, the spondylarthropathies. It is characterized by the predominance of inflammation in sacro-iliac joints, spine, and anterior chest wall. Involvement of peripheral skeletal sites, consisting of arthritis, dactylitis and enthesitis is also frequent, and extra-articular manifestations, such as uveitis, psoriasis or inflammatory bowel disease (IBD) may develop during the course of AS (1). The genetic predisposition to AS is strong, in large part due to the HLA-B27 allele (2). The burden of AS has recently been recognized as severe, frequently leading to invalidity, work loss and social impairment (3, 4). This emphasizes the need for treatments more efficacious than the non steroidal anti-inflammatory drugs (NSAIDs), which have remained the cornerstone of AS treatment until recently (5). Hence, the classical disease-modifying antirheumatic drugs with proven efficacy to treat rheumatoid arthritis (RA), such as sulphasalazine or methotrexate, exhibit at most limited efficacy, in axial AS (6).

The monoclonal antibody infliximab belongs to the anti-tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) biologic agents which have been shown as remarkably efficacious, to treat several disorders, such as RA, IBD, AS, and psoriasis (7). In AS, a dramatic response to an induction regimen consisting of 3 infusions of 5 mg/kg infliximab at weeks 0, 2, and 6, was firstly reported in open-label trials (8), then formally proven in 3-month placebo-controlled trial (9). Another trial in AS, confirmed the efficacy over placebo of an induction regimen of 5 mg/kg infliximab, followed by maintenance infusions every 6 weeks, for 6 months (10). In open-label extension trial, the initial response was sustained over 3 years in a majority of patients, by maintenance infusions every 6 weeks, whereas discontinuing infliximab predictably resulted in relapse, the delay to which varied considerably at the patient level (8, 11-13). Then, the approved standard of care for infliximab treatment

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maintenance in patient with AS is an infusion every 6 to 8 weeks, but this regimen has not been demonstrated to afford optimal benefit/risk ratio in purposely designed trial (8, 12, 13). Thus, given the potential morbidity and the heavy cost associated with infliximab treatment, some patients have been treated according to the recurrence of their symptoms, rather than on a systematic basis. In a 2-yr observational study, there was no evidence that systematic treatment provided greater benefit than on-demand treatment (13).

In RA, addition of methotrexate to infliximab was shown to improve efficacy, and also to reduce immunization against the chimeric monoclonal antibody (14). Thus, in RA it is recommended that infliximab be given in association with methotrexate. In contrast, methotrexate has generally not been administered concomitantly to infliximab in patients with AS, mostly because of the lack of evidence for methotrexate efficacy in this indication (15). Yet, it is not known if concomitant administration of methotrexate could enhance the efficacy of infliximab in AS, by preventing immunization against the chimeric antibody for instance.

The primary objective of the present study was to compare two modalities of treatment maintenance with infliximab in AS, following a standard induction regimen: systematic infusions every 6 weeks (Q6), versus on-demand infusions. Moreover, the benefit of adding methotrexate to infliximab was also evaluated.

## Patients and Methods

*Patients.* Adult patients (> 18 years old) with a diagnosis of AS were recruited for the study via 32 rheumatology departments in France. They were required to fulfill the clinical part of the modified New York criteria for the diagnosis of AS (16), and at least one of the following evidences for active inflammation, present within 3 months before inclusion: a serum C-reactive protein (CRP) level above twice the upper limit value of the normal range, a positive magnetic resonance imaging of the spine or sacro-iliac joints, a vascularized enthesitis by power-Doppler ultrasound technique (17). Additional criteria for inclusion were the presence of clinically active axial disease, as defined by 1) a Bath AS Disease Activity Index (BASDAI) (18) of  $\geq 3/10$ , and 2) a score of  $\geq 3/10$  for axial pain (second item of BASDAI). Advanced radiographic sacro-iliitis was not mandatory for inclusion in the study, but grading of sacro-iliac joints radiographic abnormalities on a pelvic X-ray taken less than 6 months before inclusion was recorded.

Disease-modifying antirheumatic drugs (DMARDs), such as sulphasalazine, methotrexate, hydroxychloroquine, intra-muscular gold, thiol compound, cyclosporin, intravenous bisphosphonate had to be discontinued for at least 4 weeks before inclusion. Dosages of NSAIDs and corticosteroid were required to remain stable for at least 4 weeks before inclusion.

A negative pregnancy test result was required for non menopausal female patients, and contraception during the study period and for six months after the last infusion of infliximab was requested of all patients of childbearing potential.

Exclusion criteria included pregnancy, breastfeeding, vaccination with a live organism during the last month, present infection or any episode of serious infection within the last three months, active malignancy within the previous five years, alcohol or drug addiction, severe chronic

concomitant disease, administration of an investigational drug within the last three months, or of any known TNF inhibitor therapy in the past (such as thalidomide, infliximab or etanercept).

*Study design.* This prospective, randomized, multicenter, 1-year, comparative study was conducted in accordance with the Declaration of Helsinki (1964) and its revision (1975), and was approved by the Institutional Review Board of the Ambroise Paré Hospital (Boulogne-Billancourt, France). Patients entered the study after reading and signing an informed consent form. At the inclusion visit (week 0), they were randomly affected to the Q6 or to the on-demand groups. In addition, patients in the on-demand group were randomly allocated to receive or not methotrexate. Randomization was centralized by the coordinating center and made by fax.

*Drugs administration.* All patients were scheduled to receive a loading regimen of infliximab consisting of three infusions at weeks 4, 6, and 10. Thereafter, patients in Q6 group received infliximab infusion every 6 weeks, until week 52, whereas patients in on-demand group received supplementary infusion only upon relapse, up to week 54, with keeping a minimum interval of 4 weeks between 2 infusions. For each infusion, infliximab was administered intravenously at a standard dose of 5 mg/kg in 250 ml NaCl 0.9%, over a 2-hour period. The dose of infliximab was increased to 7.5 mg/kg per infusion in Q6 group, starting not earlier than week 40, for those patients being in relapse at two consecutive visits. Likewise, infusion dose was increased to 7.5 mg/kg in on-demand group, starting not earlier than with the fourth on-demand infusion, if relapse occurred as early as 3 weeks after an infusion. In the group receiving methotrexate, this drug was given orally as a single weekly dose. A starting dose of 2.5 mg of methotrexate was given 4 weeks before the first infliximab infusion, and then increased weekly by 2.5 mg, up to a maximum dose of 12.5 mg which was to be continued throughout the study.

*Monitoring of relapse.* Starting at inclusion, all patients were required to call once every week-end until completion of the study, a free-toll automatic phone server, and to perform guided self-evaluation as follows. First, patients gave a positive or negative answer to the following questions: "since the last connection, do you think that your disease has remained under control?", and "since the last connection, do you think that your disease has been worsening?". Then, patients answered to the French version of BASDAI score questions, using 11-point numerical rating scales (NRS). Finally, they entered an 11-point NRS value corresponding to their global estimate of pain over the last week. Relapse was defined as a negative answer to the first question, and a positive answer to the second question, and either an increase in BASDAI score of  $\geq 1/10$ , or an increase in global pain score of  $\geq 2/10$ , as compared to the lowest score values ever reached by that patient, since the first infliximab infusion. Whenever relapse was detected  $\geq 4$  weeks after the last infusion in on-demand group, patient was urged to contact his treating center to schedule an infusion as soon as possible. A warning message was also sent to the treating center to plan an infusion for that patient over the next coming week.

*Efficacy end points.* Patient status was assessed at the occasion of each of the following visits to the treating center: inclusion (week 0), weeks 4, 6, 10, 16, and 58 in all groups, other planned infusion visits in Q6 group, and additional infusion visits determined according to relapse in on-demand group.

The following clinical variables were evaluated at each visit: patient global assessment of pain (11-point NRS), patient global assessment of disease activity (11-point NRS), French 11-point NRS versions of BASDAI, and Bath AS Disease Functional Index (BASFI; (19)), weight, Schober test, fingers-to-floor test, occiput-to-wall test, chest expansion; Westergren's erythrocyte



sedimentation rate (ESR) in the first hour, and serum CRP level. The short form (SF)-36 health-related questionnaire was used to assess quality of life at weeks 0, 16, and 58 (20).

The primary end point was the proportion of patients with a 20% improvement response according to the criteria of the ASsessment in Ankylosing Spondylitis (ASAS) International Working Group (ASAS20 responders), at week 58 (21). An ASAS20 responder was defined as a patient showing at least 20% improvement from baseline (week 0) and an absolute improvement from baseline of at least 1 unit (on a scale of 0-10), in 3 of the 4 following ASAS domains: patient's global assessment of disease activity, global assessment of pain, BASFI, and inflammation (mean of the two morning stiffness-related BASDAI score questions), and an absence of deterioration from baseline by  $\geq 20\%$  and by  $\geq 1$  unit in the fourth domain.

Secondary outcome measures included achievement of the ASAS40 response (22), and of a partial remission (21), according to ASAS definition. The ASAS40 response was computed in a manner similar to that used to compute the ASAS20 response, except that it required improvement of 40%, in at least 3 of the 4 ASAS domains, with a positive change of at least 2 units (on a scale of 0-10) in each domain. Absence of deterioration in the remaining domain was required and was defined as for the ASAS20 response. Partial remission has been defined as a value of less than 2 units (on a scale of 0-10) in each of the 4 ASAS domains (patient's global assessment, pain, BASFI, and inflammation).

Other outcome measures were improvement in independent components of the ASAS response criteria, the BASDAI, SF-36, Schober test, fingers-to-floor test, chest expansion score, and occiput-to-wall measurement, acute-phase reactants (ESR and CRP level), number of infliximab infusions administered after the loading regimen, number of patients requiring an increase in the

dose of infliximab, and the area under the curves (AUCs) of the BASDAI and global pain scores recorded on a weekly basis on automatic phone server, calculated from week 0 through week 58.

*Evaluation of safety.* Patients were monitored for adverse reactions, and vital parameters during each infusion, and for one hour afterward. At each visit, patients were asked for side effects and peripheral blood white cells count, hemoglobin level and platelets count were determined.

Additional monitoring for patients receiving methotrexate, consisted of peripheral blood white cells count, hemoglobin level and platelets count weekly for 3 months, then monthly, and creatinemia, bilirubinemia, serum aminotransferases, albuminemia, on a monthly basis.

*Statistical analysis.* Sample size determination was based on earlier trials in patients with AS (9, 23). Power calculations indicated that a sample size of 234 patients, with equal allocation to Q6 and on-demand, provided 80% power to detect a 19% difference in response rate, assuming a response rate of 53% in Q6 group and 34% in on-demand group, a 10% lost-to-follow-up rate, and using a 2-sided chi-square test with a 0.05 significance threshold.

All patients who were enrolled in the study were included in intent-to-treat analyses of efficacy and safety. The last observation carried forward approach was used to handle missing data. The AUCs of BASDAI and global pain score recorded on a weekly basis on automatic phone server, were computed using a trapezoidal rule. Quality of life was assessed in each group by computing a quality-adjusted time without symptoms and toxicity (Q-Twist) analysis, as previously described (24, 25), with some modifications to account for the specific purpose of this study. Whatever the length of follow-up, time spending in the study from week 10 through week 58 was divided into several possible health states: (i) time without symptoms and toxicity (TWIST), i.e. low disease symptoms (BASDAI  $\leq$  3.5, (26)); (ii) discomfort (DIS) related to an infusion, set to 3 days; (iii)

moderate relapse (REL1:  $3.5 < \text{BASDAI} \leq 5.5$ );(iv) serious relapse (REL2:  $5.5 < \text{BASDAI} \leq 7.5$ ); (v) very severe relapse (REL3:  $\text{BASDAI} > 7.5$ ). Percentage of time spent in each health state was weighted by an utility coefficient (denoted as a U), which was arbitrarily defined to account for distinct levels of quality of life relative to TWIST (UTWIST = 1), in the health states DIS (UDIS = 0.75, or 0.5 in case of adverse event related to the infusion), REL1 (UREL1 = 0.90), REL2 (UREL2 = 0.75), and REL3 (UREL3 = 0.50). The Q-Twist was computed as follows:  $Q\text{-Twist} = \text{TWIST} + \text{UDIS} * \text{DIS} + \text{UREL1} * \text{REL1} + \text{UREL2} * \text{REL2} + \text{UREL3} * \text{REL3}$ .

Differences between groups were tested by chi-square test (categorical data), or Student's unpaired t test (numerical data). A *P* value < 0.05 was considered significant. All statistical analysis were performed using SAS 9.1 (SAS Institute, Cary, NC).

## Results

*Patients.* Overall, 247 patients with an active axial AS were included in the study between april and october 2003, and randomly assigned to receive infliximab as a continuous treatment (Q6, 124 patients), or only upon relapse (on-demand, 123 patients), after a standard loading regimen of 3 infusions. In on-demand group, patients were randomly allocated to receive methotrexate (61 patients) or not (62 patients) throughout the study, starting 4 weeks before the first infusion of infliximab (Figure 1). Characteristics of the patients at entry were typical of AS (Table 1), with an age (mean  $\pm$  SD) of  $41.4 \pm 11.3$  years, a disease duration of  $14.9 \pm 9.9$  years, and a majority of males (76%), being HLA-B27 positive (80%), and having advanced radiographic sacroiliitis (79%). A majority of them (76%) also had previously received DMARDs, mostly sulphasalazine (70%), or methotrexate (36%), and were receiving stable dose of NSAID at inclusion (82%). They had active axial disease, as shown by a global assessment of disease activity of  $7.4 \pm 1.6$ , a score of BASDAI of  $6.2 \pm 1.4$ , a score of axial pain on BASDAI of  $7.3 \pm 1.7$ , an ESR of  $34.3 \pm 23.3$  mm, and a CRP value of  $31 \pm 24.5$  mg/L. The treatment groups were well matched with regard to characteristics at inclusion (Table 1).

All the patients who had been included, except 6, received at least 1 infusion of infliximab, and a majority of them (72%) completed the one-year trial. Reasons for discontinuation are summarized in Figure 1, and were well balanced between treatment groups. The overall rate of weekly connections to the automatic phone server throughout the study was 88% of the theoretical connections expected according to intent-to-treat analyses. In on-demand group, 110 patients received  $\geq 1$  infusion(s) of infliximab after the loading regimen, because of relapse detected by automatic phone server, resulting in 432 on-demand infusions. The delay between decision and execution of on-demand infusion was 4.3 days on average, and  $\leq 7$  days in 90% of

cases. In this group, only 3 of 85 patients (3.5%) who completed the study did not require on-demand infusion because of relapse (1 without, and 2 with methotrexate).

*Efficacy.* At week 58, 93 of 124 patients (75%) in the Q6 group were ASAS20 responders, compared with 56 of 123 patients (46%) in the on-demand group ( $P < 0.0001$ ) (Table 2).

Significantly more patients were also ASAS40 responders, and fulfilled ASAS criteria for partial remission in Q6 group than in on-demand group (Table 2). In the latter group, proportions of ASAS20, and ASAS40 responders, and of patients in partial remission were not significantly different between patients who received methotrexate, and those who did not (Table 2). A subgroup analysis restricted to patients who fulfilled the modified New York criteria yielded similar results (not shown).

Besides ASAS criteria, intention-to-treat analysis of most other secondary criteria, at week 58, displayed a significantly better response in Q6 than in on-demand group, whereas there was no statistically significant difference between patients with and without methotrexate in on-demand group (Table 3). A greater increase in weight between inclusion and week 58 was also noticed in Q6 than in on-demand group (Table 3).

The AUCs of the weekly BASDAI and global pain score, recorded throughout the study on automatic phone server were lower in Q6 than in on-demand group ( $3.5 \pm 1.8$  vs.  $4.2 \pm 2.1$ ,  $P = 0.004$ ; and  $4.0 \pm 1.8$  vs.  $4.6 \pm 2.1$ ,  $P = 0.02$ , respectively). In contrast, those AUCs were not different between patients with and without methotrexate in on-demand group ( $4.2 \pm 2.1$  vs.  $4.2 \pm 2$ ,  $P = 0.95$ ; and  $4.6 \pm 2.2$  vs.  $4.5 \pm 2.1$ ,  $P = 0.91$ , respectively).

After the loading regimen, a greater number of infliximab infusions were administered in Q6 group, than in on-demand group, throughout the study period ( $5.8 \pm 2.2$  vs.  $3.5 \pm 2.3$ ,  $P <$

0.0001) (Table 4). No difference in infusions number was observed in on-demand group, between patients with and without methotrexate ( $3.3 \pm 2.0$  vs.  $3.7 \pm 2.6$ ,  $P = 0.38$ ) (Table 4). An increase in infliximab dose to 7.5 mg/kg per infusion, because of insufficient response, was required for 6 patients each in Q6 (4.8%) and in on-demand (4.9%) groups ( $P = 0.99$ ) (Table 4). In the latter group, 2 of the patients were on methotrexate (3.3%), and 4 were not (6.5%) ( $P = 0.41$ ) (Table 4).

*Safety.* The number of patients experiencing adverse event was 218 (88.3%), without difference between groups. Sixty-six serious events occurred in 57 patients, including 1 sudden death, attributed to likely myocardial infarction, in the on-demand group receiving methotrexate, and 2 solid cancers (1 in the Q6 group, and 1 in the on-demand group with methotrexate). There were 3 cases of serious infection in the Q6 and 4 in the on-demand groups (3 patients with, and 1 without methotrexate). Other non-serious infections affected significantly more patients in Q6, than in on-demand group (59.7% vs. 45.5%;  $P = 0.03$ ), and their overall frequency was increased in Q6, as compared to on-demand group (mean  $\pm$  SD:  $1.47 \pm 1.85$  vs.  $0.86 \pm 1.22$ ;  $P = 0.003$ ), without difference related to methotrexate intake. Notably, there was no case of lymphoma, tuberculosis or opportunistic infection. Reaction to infusion was noticed in a greater proportion of patients in Q6 group, than in on-demand group (Table 4), but the proportion of infusions complicated with reactions was not different between both groups. In the on-demand group, there was no statistically significant difference, either in the proportion of patients, nor in the proportion of infusions complicated with reactions between patients with and without methotrexate (Table 4).

*Q-Twist.* Percentage of time spending in the TWIST state was higher in the Q6 group than in the on-demand group (Figure 2). The Q-Twist value was significantly greater in the Q6 group than in the on-demand group ( $91.7 \pm 8.9$  vs  $87.6 \pm 12.5$ ;  $P = 0.003$ ).

## Discussion

Despite the great efficacy of infliximab to treat AS, it has not yet been shown that the treatment modality recommended for this drug as a standard of care, i.e. an induction regimen consisting of 3 infusions of 5 mg/kg of infliximab, followed by infusions every 6 to 8 weeks, warranted the best efficacy/safety ratio. Inconvenience associated to infliximab therapy include safety concern, discomfort related to infusion procedure, and cost of the treatment (27). This is why it is of most interest to examine which dose and/or rhythm of infliximab infusions afford optimal treatment to each patient. Several studies have evaluated the efficacy of a reduced infusion dose of 3 mg/kg infliximab, administered as a standard loading regimen, followed by re-infusions every 8 weeks, as recommended to treat RA (28-31). Reduced infliximab dose could adequately control a subset of patients (28-30), but in one of the studies the dosage of infliximab and/or the frequency of infusions had to be increased to maintain sufficient efficacy, so that there was no real gain at the end of follow up, as compared to a standard regimen (31). Furthermore, in none of those studies was the low-dose infliximab compared to a standard regimen, so that besides lowering the cost of treatment, there is no proven advantage, either in terms of efficacy or safety, of reducing the dose of infliximab.

In AS, perception by the patient himself of major disease symptoms, i.e. fatigue, pain and stiffness, is considered as a very good indicator of disease activity. Self-administered questionnaires, such as the BASDAI are routinely used to evaluate anti-TNF therapy efficacy (32). Thus, considering the rapid kinetics of effect of infliximab on patients symptoms, and its high variability at patient's level, both during the induction phase of treatment and during relapse, we reasoned that it could be beneficial to adapt intervals between infusions to patients symptoms,



rather than to modify the dose administered per infusion (8, 13). This could offer the advantage of adjusting the amount of infliximab delivered, to the exact requirement of each patient. To achieve this goal, we set a remote survey system based on two indicators of disease activity, i.e. global pain, and BASDAI, which allowed us to detect as early as possible a worsening of disease activity. Cut-off values which were used to identify a relapse, are very similar to those recently recognized as the minimum clinically relevant level of change of these outcomes measures (33). Furthermore, the delay between detection of a relapse, and administration of on-demand infliximab infusion was remarkably short, i.e. 4 days on average. Thus, suitable conditions were achieved to assess the advantage of adapting the rhythm of infusions to each patient.

Previous work had shown that relapse occurred upon infliximab discontinuation in most, if not all, AS patients (12, 13). Indeed, in the present study, the vast majority of patients in on-demand group required at least one additional infusion after the loading regimen, but during the same period of time, the number of infusions was reduced by 40% in this group, as compared to the Q6 group. Accordingly, the proportion of patients experiencing reaction to infusion, and the rate of non-serious infectious events were 55%, and 41.5% lower in the on-demand group, than in the Q6 group, respectively. Even though, the rate of serious adverse events, including infections, or the overall frequency of adverse events were not significantly different between groups.

A major finding of this study was the remarkable superiority of infliximab given at fixed interval over on-demand regimen. This result involved all parameters studied after one year of treatment, except for physical SF-36 component, including the frequency of responders using ASAS criteria, physical examination tests, and biological markers of inflammation. Between-groups difference was observed not only at the end of the study, but also on the weekly evaluation of criteria, the raise of which was used to validate relapse i.e. BASDAI, and global appreciation of

pain. This suggests that patients failed to properly identify relapses or deliberately delayed their notification, presumably to minimize the inconvenience of infusions. Whatever the reason, there was a progressive divergence of the weekly BASDAI between Q6 and on-demand groups over one year (data not shown), resulting in a rather poor response rate in the on-demand group at the end of the trial. We used the Q-Twist method, as an attempt to estimate a balance between the advantage of sparing infusions and the disadvantage of reduced efficacy, associated with on-demand infusions. This calculation allowed us to conclude to the superiority of infliximab given at fixed interval. Noteworthy, patients in the on-demand group spent almost twice as much time overall, in serious or very severe relapse state, than those in the Q6 group.

Methotrexate or other immunosuppressive therapies, such as azathioprine, are routinely combined to infliximab for the treatment of diseases such as RA and Crohn's disease, resulting in a greater efficacy, because of additional efficacy on the disease, and/or prevention of immunization against infliximab chimeric antibody (14, 34). Thus, we also tested the advantage of adding methotrexate to infliximab for AS treatment. Given that methotrexate alone is not efficacious to treat AS, even at dose as high as 20 mg/week (15, 35), we chose an intermediate dose of methotrexate which was progressively reached, in order to minimize the risk of side-effect due to this drug (36), while trying to prevent immunization and reaction to infliximab which are often associated with a loss of efficacy (37-39). Hence, adverse-events were not increased among patients taking methotrexate. Furthermore, there was a trend towards fewer reactions to infusions in the group treated with methotrexate, as compared to the on-demand group without methotrexate, which could indicate that addition of methotrexate actually prevented immunization against infliximab, but the difference was not statistically significant. Nevertheless, efficacy was not improved by the combination with methotrexate, as judged either on disease parameters or on

the number of on-demand infusions required by patients. Thus, in this study, combination of methotrexate and infliximab provided no demonstrable benefit. Such negative result could however be explained by a lack of power to demonstrate a limited efficacy of methotrexate, since the sample size was not primarily determined to answer this question.

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**Table 1.** Characteristics of the study patients at inclusion, by treatment group\*

Characteristic	Q6 (n = 124)	On demand		
		All (n = 123)	MTX- (n = 62)	MTX + (n = 61)
Males, no. (%)	93 (75)	95 (77)	50 (81)	45 (74)
Age, years	41.4 ± 12.3	41.3 ± 10.3	42.7 ± 10.9	40 ± 9.6
Disease duration, years	14.6 ± 10.5	15.1 ± 9.3	16.4 ± 11.1	13.8 ± 7
HLA-B27 positive, % †	80	81	79	83
Sacroiliitis, % ‡	76	82	83	81
History of peripheral arthritis, no. (%)	73 (59)	82 (67)	36 (58)	46 (75)
History of uveitis, no. (%)	33 (27)	43 (35)	23 (37)	20 (33)
History of psoriasis, no. (%)	20 (16)	13 (11)	9 (15)	4 (7)
History of IBD, no. (%)	12 (10)	12 (10)	6 (10)	6 (10)
Global pain (NRS)	6.9 ± 1.9	6.7 ± 1.8	6.6 ± 2.0	6.9 ± 1.6
Patient's global assessment (NRS)	7.4 ± 2.9	7.5 ± 1.5	7.3 ± 1.4	7.7 ± 1.6
BASDAI	6.2 ± 1.5	6.2 ± 1.3	6.3 ± 1.3	6.1 ± 1.4
BASFI	5.4 ± 2	5.8 ± 1.9	5.6 ± 1.9	6.0 ± 1.8
SF-36 physical component	33 ± 7	31 ± 7	30 ± 6	32 ± 7
SF-36 mental component	34 ± 10	36 ± 10	35 ± 9	37 ± 11
ESR (mm)	37 ± 25	32 ± 21	31 ± 23	33 ± 19
CRP level (mg/L)	33 ± 27	29 ± 21	28 ± 22	31 ± 22
Weight (kg)	73 ± 16	73 ± 14	73 ± 14	73 ± 13
Schober test (cm)	2.2 ± 1.5	2.5 ± 1.5	2.6 ± 1.7	2.3 ± 1.4
Fingers-to-floor (cm)	28 ± 15	30 ± 16	29 ± 17	31 ± 16
Occiput-to-wall (cm)	6.2 ± 6.9	6.1 ± 6.7	6.3 ± 6.5	5.9 ± 7.0
Chest expansion (cm)	3.6 ± 1.9	3.5 ± 1.9	3.6 ± 1.8	3.4 ± 2.0

\* Except where indicated, values are mean ± SD. No statistically significant between-group difference was found for any baseline characteristic by chi-square test (categorical data), or Student's t test (numerical data). IBD = inflammatory bowel disease; NRS = numerical rating scale; BASDAI = Bath ankylosing spondylitis activity index; BASFI = Bath ankylosing spondylitis functional index; SF-36 = short form-36; ESR = erythrocyte sedimentation rate; CRP = C reactive protein; MTX = methotrexate.

† The number of patients evaluated in each group was 115, 110, 52, and 58, respectively.

‡ Radiographic sacroiliitis of at least bilateral grade II or unilateral grade III. The number of patients evaluated in each group was 118, 111, 54 and 57, respectively.

**Table 2.** Proportion of patients who achieved response at week 58, according to the ASAS criteria, by treatment group (intention-to-treat analysis) \*

ASAS criteria	Q6 (n = 124)	Responders at week 58					P †
		On-demand All (n = 123)	On-demand MTX- (n = 62)	On demand MTX + (n = 61)	P †		
ASAS20	93 (75)	56 (46)	25 (40)	31 (51)	0.24		
ASAS40	63 (51)	37 (30)	15 (24)	22 (36)	0.15		
Partial remission	34 (27)	9 (7)	3 (5)	6 (10)	0.32		

\* Values are the numbers (%) of patients responding to the criteria; ASAS = ASessment in Ankylosing Spondylitis (see Patients and Methods for explanation of ASAS Working Group criteria).

† P values determined by chi-square test.

**Table 3.** Clinical and biological criteria change from inclusion to week 58, by treatment group (intention-to-treat analysis) \*

Criterion	Q6 (n = 124)	On-demand All (n = 123)	Q6 vs. on-demand <i>P</i> †	On-demand MTX- (n = 62)	On demand MTX + (n = 61)	MTX- vs. MTX+ <i>P</i> †
Global assessment of pain (NRS)	- 3.1 ± 2.8	- 1.4 ± 2.6	< 0.0001	- 1.3 ± 2.7	- 1.6 ± 2.6	0.43
Disease activity by patient (NRS)	- 3.3 ± 2.9	- 2.0 ± 2.4	0.0003	- 2.1 ± 2.4	- 2.9 ± 2.6	0.38
BASDAI	- 2.9 ± 2.4	- 1.7 ± 2.0	< 0.0001	- 1.8 ± 1.8	- 1.6 ± 2.1	0.57
BASFI	- 2.4 ± 2.3	- 1.2 ± 2.0	< 0.0001	- 1.0 ± 1.9	- 1.5 ± 2.0	0.23
SF-36 physical component	6.0 ± 9.1	5.7 ± 8.1	0.85	5.8 ± 8.3	5.7 ± 8.0	0.93
SF-36 mental component	7.8 ± 10.2	4.8 ± 9.4	0.02	5.8 ± 10.0	3.9 ± 8.8	0.29
ESR (mm)	- 18.6 ± 24.9	- 10.4 ± 17.8	0.003	- 9.1 ± 17.7	- 11.7 ± 17.9	0.43
CRP (mg/L)	- 20.2 ± 25.4	- 8.1 ± 28.0	0.0004	- 6.7 ± 30.6	- 9.4 ± 25.1	0.59
Weight (kg)	2.4 ± 4.6	0.9 ± 4.2	0.009	0.9 ± 3.9	0.9 ± 4.5	0.99
Schober test (cm)	0.6 ± 1.1	0.3 ± 1.5	0.06	0.2 ± 1.5	0.3 ± 1.5	0.66
Finger-to-floor (cm)	- 6.7 ± 10.7	- 2.9 ± 14.5	0.02	- 1.6 ± 15.8	- 4.2 ± 13.0	0.32
Occiput-to-wall (cm)	- 1.4 ± 3.3	0 ± 4.4	0.006	0.1 ± 5.0	- 0.2 ± 3.8	0.70
Chest expansion (cm)	0.7 ± 1.6	0.7 ± 1.7	0.96	0.7 ± 1.7	0.7 ± 1.7	0.90

\*Values are mean  $\pm$  SD. See Patients and Methods for a description of the study groups. NRS = numerical rating scale; BASDAI = Bath ankylosing spondylitis activity index; BASFI = Bath ankylosing spondylitis functional index; SF-36 = short form-36; ESR = erythrocyte sedimentation rate; CRP = C reactive protein. --; MTX = methotrexate.

† *P* values determined by student's *t* test.

**Table 4.** Infliximab infusions \* (intention-to-treat analysis)

Parameter	Treatment group					
	Q6 (n = 124)	On-demand All (n = 123)	P	On-demand MTX- (n = 62)	On demand MTX + (61)	P
Infusions no. after week 10, mean $\pm$ SD	5.8 $\pm$ 2.2	3.5 $\pm$ 2.3	<0.0001 †	3.7 $\pm$ 2.6	3.3 $\pm$ 2.0	0.38 †
Reactions to infusion						
Relative to patients, no. (%)	18 (14.5)	8 (6.5)	<0.04 ‡	6 (9.7)	2 (3.3)	0.27 ‡
Relative to infusions, mean % $\pm$ SD	2.8 $\pm$ 8.7	1.4 $\pm$ 5.7	0.12 †	1.8 $\pm$ 6.4	0.9 $\pm$ 5.0	0.37 †
Patients requiring increase of infusion dose to 7.5 mg/kg, no. (%)	6 (4.8)	6 (4.9)	0.99 ‡	4 (6.5)	2 (3.3)	0.41 ‡

\* MTX = methotrexate.

† P values determined by student's t test.

‡ P values determined by chi-square test.

## Figure legends

**Figure 1.** Randomization, reasons for treatment discontinuation, and number of patients who completed the 58 week study of infliximab therapy for ankylosing spondylitis. Two hundred and forty-seven patients were initially enrolled, 6 of whom did not receive an infusion of study medication. Hundred and seventy seven patients completed the study protocol. Sixty-four patients discontinued the study, 27 because of adverse events, 13 because of lack of efficacy, and 24 because of personal reasons or non compliance.

**Figure 2.** Percentage of time spending in the study from week 10 through week 58, according to health status in the 2 infliximab maintenance groups: on-demand infusions, or infusions at fixed interval (Q6). TWIST: low disease activity ( $BASDAI \leq 3.5$ ); DIS: discomfort related to an infusion; REL1: moderate relapse ( $3.5 < BASDAI \leq 5.5$ ); REL2: serious relapse ( $5.5 < BASDAI \leq 7.5$ ); (v) REL3: very severe relapse ( $BASDAI > 7.5$ ).





