

Temporal Dissociation between Disease Activity Reduction and Improvements in Fatigue and Physical Function After Infliximab in Rheumatoid Arthritis

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Abstract

Objective: To evaluate the temporal responses to infliximab in fatigue and other selected parameters of physical function, inflammation, disease activity, and QOL in a cohort of rheumatoid arthritis patients.

Methods: A prospective study was conducted. At baseline (PRE), after two (POST 2) and six (POST 6) months of treatment with infliximab (3 mg/Kg), fatigue, muscle function and strength, quality of life, disease activity, and markers of inflammation were assessed in 25 consecutive patients.

Results: Infliximab treatment resulted in a significant reduction in fatigue at POST 2 and POST 6 when evaluated by both Chalder and the Global Fatigue VAS scale. Similarly, improvements in physical function at POST 2 and POST 6 as assessed by both the timed-stands test and SF-36 physical functioning domain was also observed. Conversely, disease activity, as assessed by DAS-28, remained unchanged at POST 2 and improved only at POST 6. The reduction in clinical markers of inflammation (i.e. CRP and ERS) did not reach significance at POST 2 or at POST 6, except for a trend in CRP after 6 months of treatment. Muscle strength remained unchanged throughout the trial. Additionally, no significant correlations were found between delta changes of either disease activity or inflammation parameters and physical function and fatigue parameters.

Conclusion: These findings clearly reveal a temporal dissociation between the improvements in fatigue, physical function, and quality of life and the reduction in disease activity in response to infliximab in rheumatoid arthritis patients. The predictive value of these early response factors merits further investigations.

Keywords: TNF- α blockers; Early response; Biologic therapy

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by swollen of the joints, pain, impaired muscle strength, physical function, and fatigue [1,2]. The latter symptom is believed to impose severe physical limitation to the patients, thereby impacting their quality of life (QOL) [3].

Fatigue has been recognized as a multi-causal, multidimensional and complex concept in which psychological, biochemical, and physiological factors play a role [4]. In RA, little is known regarding the time-course of the effects of biologic medication on fatigue and its relationship with functional capacity, muscular strength, and QOL, as well as disease activity and inflammatory parameters [5].

Therefore, the purpose of this study was to evaluate the temporal responses to infliximab in fatigue and other selected parameters of physical function, inflammation, disease activity, and QOL in a cohort of RA patients.

Patients and Methods

Study design

A prospective study was conducted. At baseline (PRE), after two (POST 2) and six (POST 6) months of treatment with infliximab (3 mg/Kg), we assessed fatigue, muscle function and strength, quality of life, disease activity, and markers of inflammation.

Patients

Twenty-five consecutive RA patients (22 women; mean age: 49.2 ± 12.6 years; mean time since diagnosis: 9.8 ± 6.2 years) were selected from the Division of Rheumatology of the School of Medicine of the University of São Paulo, Brazil. Inclusion criteria were: diagnosis of RA, according to the American College of Rheumatology (1987) criteria; age between 18 and 65 years; and active disease despite treatment with at least two of DMARDs including MTX. Patients unable to perform physical tests were excluded from the study. According to our Biological Center Protocol, the anti-TNF initiation was followed by the DMARDs withdrawal, except methotrexate (60%), leflunomide (30%) and azathioprine (10%). Glucocorticoid was maintained (median dose 8 ± 3.83 mg/d; range 5-20 mg/d). The

protocol was approved by the local ethical committee and all patients signed the informed consent prior to participation.

Fatigue, quality of life, inflammation and disease activity

Chalder questionnaire and Global Fatigue VAS scale were used to assess fatigue [6]. Additionally, the patients completed the HAQ and HAQ-ID to evaluate functional capacity, and the SF-36 to assess quality of life [7]. Disease activity was evaluated by the Disease Activity Score (DAS-28) [8]. The systemic inflammation markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also assessed at all time points.

Physical function and muscle strength

Physical function was assessed by the timed-stands test [9]. Maximal isometric strength was evaluated through the use of a handgrip and a trunk extension dynamometer. Maximal dynamic strength was determined by means of the one-repetition-maximum test (1-RM) on the leg-press and bench-press exercises [10].

Statistical analysis

Data were analyzed by a one-way ANOVA. Univariate Person's correlations between delta changes of disease activity (DAS-28) or inflammation parameters (ESR and CRP) with fatigue (Chalder and Score of Global Fatigue) and physical function (Timed-Stands Test) was performed. Significance level was set at $p \leq 0.05$. Data are presented as mean \pm SE.

Results

Table 1 summarizes the main results. Infliximab treatment resulted in a significant reduction in fatigue at POST 2 and POST 6 when evaluated by both Chalder and the Global Fatigue VAS scale. Similarly, improvements in physical function at POST 2 and POST 6 were also observed, as assessed by both Timed-Stands Test and SF-36 physical functioning domain. Conversely, disease activity (as assessed by DAS-28) remained unchanged at POST 2 and improved only at POST 6. The reduction in clinical markers of inflammation (i.e. CRP and ESR) did not reach significance at POST 2 or at POST 6, except for a trend in CRP after 6 months of treatment.

	PRE	POST 2	POST 6	<i>p</i> (PRE to POST 2)	<i>p</i> (PRE to POST 6)
Chalder	17.76 \pm 1.31	6.41 \pm 0.86	6.40 \pm 0.78	<0.0001	<0.0001
Global Fatigue VAS scale	6.76 \pm 0.37	3.72 \pm 0.54	3.92 \pm 0.34	<0.0001	<0.0001
Timed-Stands test (number of stands)	8.96 \pm 1.12	13.08 \pm 0.90	13.40 \pm 1.26	0.03	0.01
SF-36 physical functioning	21.2 \pm 3.91	71.72 \pm 5.87	93.60 \pm 2.49	<0.0001	<0.0001
SF-36 role-physical	38.64 \pm 4.78	82.45 \pm 6.21	89.20 \pm 4.58	<0.0001	<0.0001
SF-36 bodily-pain	36.76 \pm 3.05	60.56 \pm 4.11	60.16 \pm 3.48	<0.0001	<0.0001
SF-36 general-health	41.16 \pm 3.31	69.28 \pm 3.87	62.56 \pm 3.40	<0.0001	<0.0001
SF-36 vitality	43.40 \pm 4.11	73.40 \pm 4.59	61.00 \pm 3.35	<0.0001	0.0008
SF-36 social-functioning	54.00 \pm 4.71	64.80 \pm 4.06	78.42 \pm 3.68	0.16 (ns)	0.0002
SF-36 role-emotional	47.96 \pm 5.12	79.98 \pm 6.08	83.99 \pm 5.81	0.0005	<0.0001
SF-36 mental-health	60.72 \pm 4.34	69.16 \pm 5.54	68.36 \pm 2.89	0.37 (ns)	0.44 (ns)
DAS-28	4.90 \pm 0.29	4.38 \pm 0.36	3.2 \pm 0.42	0.47 (ns)	0.004
CRP (mg/L)	19.61 \pm 4.76	9.29 \pm 2.29	9.02 \pm 2.00	0.08 (ns)	0.06 (ns)
ESR (mm/1st h)	32.52 \pm 6.16	25.86 \pm 4.33	19.21 \pm 3.35	0.45 (ns)	0.11 (ns)

Table 1: Fatigue, physical function, disease activity, and inflammation parameters before (PRE), after two (POST 2) and after six (POST 6) months of infliximab treatment. PRE: before infliximab treatment; POST 2: after 2 months of treatment; POST 6: after 6 months of treatment; DAS: disease activity score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. Muscle strength remained unchanged throughout the study ($p=0.22$ for bench-press 1-RM; $p=0.19$ for leg-press 1-RM; $p=0.14$ for handgrip; $p=0.69$ for trunk extension).

Additionally, no significant correlations were found between delta changes of either disease activity or inflammation parameters and physical function and fatigue parameters (Table 2).

Discussion

The novel finding of this study is the temporal dissociation between the improvements in fatigue, physical function, and quality of life and the reduction in disease activity in response to infliximab in RA patients.

		DAS-28 (r)	ESR (r)	CRP (r)
Chalder	PRE to POST 2	0.02	0.05	0.10
	PRE to POST 6	0.22	0.02	0.08
Global Fatigue VAS scale	PRE to POST 2	0.19	-0.22	-0.06
	PRE to POST 6	-0.01	0.09	0.15
Timed-Stands Test	PRE to POST 2	0.14	-0.28	-0.32
	PRE to POST 6	-0.26	-0.16	-0.27

Table 2: Person correlation (r) between delta changes of disease activity (DAS-28) or inflammation parameters (ESR and CRP) with fatigue (Chalder and Score of Global Fatigue) and physical function (timed-stands test). Values are presented as correlation from delta changes between PRE and POST 2 and changes between PRE and POST 6 time points. PRE: before infliximab treatment; POST 2: after 2 months of treatment; POST 6: after 6 months of treatment; DAS: disease activity score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. No significant associations were observed ($p>0.05$).

A few studies demonstrated the effect of infliximab treatment in RA [4] with a positive result on fatigue [11,12]. However, fatigue assessments were performed only after 24 weeks of treatment [11] or in patients on stable treatment for at least 6 months prior to the intervention [12]. In fact, there is evidence of an early response to other TNF α blockers (e.g., etanercept and adalimumab) in fatigue [13,14], but without a concomitant evaluation of disease activity and inflammation, precluding any conclusion about the sequence of these events. To the best of our knowledge, this is the first report to show that infliximab responses are chronologically "detached", with an early improvement in fatigue and other parameters related to quality of life and physical function, and a late improvement in disease activity and a possible attenuation in inflammation (based on a non-significant decrease in CRP values). The lack of any statistical association between these parameters reinforces this temporal dissociation.

As opposed to these findings, Ban et al. [15] observed sustained improvement in disease activity markers in 13 Asians patients with RA after only two weeks of infliximab treatment throughout a 54-week follow-up period. Interestingly, such benefits were paralleled by physical function amelioration, but no assessments of fatigue and other parameters of quality of life were performed. Ethnic differences may have accounted for the early improvement in disease activity reported in this study.

Despite the fact that the DAS-28 score is recognized as one of the most relevant criteria for assessing the efficacy of any sort of treatment in RA, the present data suggest that other factors such as fatigue, physical function and quality of life should be considered in order to fully appreciate the efficacy of infliximab treatment in RA.

In summary, the finding of a temporal dissociation among clinical parameters (e.g., fatigue and disease activity) in response to infliximab provides a novel tool to assess the effectiveness of biological therapy that may help clinicians in the daily care of RA patients. The predictive value of these early response factors merits further investigations with larger number of patients.

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Authorship information

Bruno Gualano, Hamilton Roschel, Fernanda Rodrigues Lima, Ana Lúcia de Sá Pinto, Eloísa Bonfá, and Ieda Laurindo designed the research. Camila Ventura, Guilherme Artioli, and Ieda Laurindo conducted the research. Hamilton Roschel, Bruno Gualano, Fernanda Rodrigues Lima, Ana Lúcia de Sá Pinto, Eloísa Bonfá, and Ieda Laurindo analyzed the data. Hamilton Roschel, Bruno Gualano, Guilherme Artioli, Eloísa Bonfá, and Ieda Laurindo wrote the paper.

References

1. Cooney JK, Law RJ, Matschke V, Lemmey AB, Moore JP, et al. (2011) Benefits of exercise in rheumatoid arthritis. *J Aging Res* 2011: 681640.
2. Reid A, Brady A, Blake C, Mongey AB, Veale DJ, et al. (2011) Randomised controlled trial examining the effect of exercise in people with rheumatoid arthritis taking anti-TNF α therapy medication. *BMC Musculoskelet Disord* 12: 11.
3. Michaud K, Wolfe F (2007) Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 21: 885-906.
4. Zintzaras E, Dahabreh IJ, Giannouli S, Voulgarelis M, Moutsopoulos HM (2008) Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. *Clin Ther* 30: 1939-1955.
5. Harriman G, Harper LK, Schaible TF (1999) Summary of clinical trials in rheumatoid arthritis using infliximab, an anti-TNF α treatment. *Ann Rheum Dis* 58 Suppl 1: I61-64.
6. Hewlett S, Hehir M, Kirwan JR (2007) Measuring fatigue in rheumatoid arthritis: a systematic review of scales in use. *Arthritis Rheum* 57: 429-439.
7. Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 30: 473-483.
8. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, et al. (1996) Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 39: 34-40.

9. Newcomer KL, Krug HE, Mahowald ML (1993) Validity and reliability of the timed-stands test for patients with rheumatoid arthritis and other chronic diseases. *J Rheumatol* 20: 21-27.
10. Brown LE, Weir JP. ASEP Procedures Recommendation I: Accurate Assessment of Muscular Strength and Power. *J Exerc Physiol Online* 2001;4:21.
11. Hoving JL, Bartelds GM, Sluiter JK, Sadiraj K, Groot I, et al. Perceived work ability, quality of life, and fatigue in patients with rheumatoid arthritis after a 6-month course of TNF inhibitors: prospective intervention study and partial economic evaluation. *Scand J Rheumatol* 38: 246-50.
12. van Hoogmoed D, Fransen J, Repping-Wuts H, Spee L, Bleijenberg G, et al. (2013) The effect of anti-TNF- α vs. DMARDs on fatigue in rheumatoid arthritis patients. *Scand J Rheumatol* 42: 15-19.
13. Moreland LW, Genovese MC, Sato R, Singh A (2006) Effect of etanercept on fatigue in patients with recent or established rheumatoid arthritis. *Arthritis Rheum* 55: 287-293.
14. Strand V, Rentz AM, Cifaldi MA, Chen N, Roy S, et al. (2012) Health-related quality of life outcomes of adalimumab for patients with early rheumatoid arthritis: results from a randomized multicenter study. *J Rheumatol* 39: 63-72.
15. Ban A, Inaba M, Furumitsu Y, Okamoto K, Yukioka K, et al. (2010) Time-course of health status in patients with rheumatoid arthritis during the first year of treatment with infliximab. *Biomed Pharmacother* 64: 107-112.