CTLA-4 Ig as an effective treatment in a patient with type I diabetes mellitus and seropositive rheumatoid arthritis

A.L. Fedele, S. Alivernini, E. Gremese, G. Ferraccioli

Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy.

Anna Laura Fedele, MD
Stefano Alivernini, MD, PhD
Elisa Gremese, MD
Gianfranco Ferraccioli, MD, Prof.

Please address correspondence to:
Prof. Gianfranco Ferraccioli,
Istituto di Reumatologia e Scienze Affini,
Università Cattolica del Sacro Cuore,
Complesso Integrato Columbus,
Via Giuseppe Moscati 31,
00168 Roma, Italy.
E-mail: gff1990@gmail.com

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ABSTRACT

We describe a patient suffering from seropositive rheumatoid arthritis (RA) and type I diabetes mellitus (T1DM), who achieved a good EULAR response together with an improvement of the glycemic profile under treatment with CTLA-4 Ig.

A close association is known to exist between T1DM and RA, and CTLA-4 exon 1 polymorphism has been associated to RA with coexisting autoimmune endocrinopathies. The possible common genetic background and the potential role of CTLA-4 Ig in the early phases of T1DM, could be considered in the therapeutic interventions in RA patients with type 1 diabetes.

Introduction

Abatacept is a cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion protein (CTLA-4 Ig) and it blocks the interaction of CD28-B7 during activation of naïve and activated T cells, eliciting increased cell death and anergy induction and inhibiting cell differentiation. Moreover, it modulates B-cell activity and downregulates macrophagic production of pro-inflammatory cytokines (1-4).

CTLA-4 Ig is indicated for rheumatoid arthritis (RA) patients with an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs) or anti-tumour necrosis factor (TNF) agents (5, 6).

An association between the CTLA-4 exon 1 polymorphism and RA with coexisting autoimmune endocrinopathies was demonstrated. In a cohort of early RA the prevalence of the CTLA-4 G allele among the patients with coexisting autoimmune thyroid disease (AITD) and type I diabetes mellitus (T1DM) was significantly different from that of RA without endocrinopathy (7). Moreover, a close association has been found between T1DM and seropositive RA with an odds ratio of 4.9 (8).

A crucial involvement of co-stimulation in T1DM pathogenesis has been demonstrated in a randomised controlled trial, in which CTLA-4 Ig slowed decline of beta cell function and improved HbA1c over two years in patients with recent-onset T1DM (9). The beneficial effect was sustained for at least 1 year after CTLA-4 Ig cessation (10). Moreover, a case report has described an improvement in insulin resistance after short-term treatment with CTLA-4 Ig in RA patients with T2DM, probably through a modulation of adipose tissue infiltrating T cells (11).

Clinical case description

We describe a 45-year-old Caucasian woman suffering from rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) seropositive and erosive RA since 1994. As comorbidity, T1DM was diagnosed one year before and she was receiving 20 UI daily of short-acting insulin and 12 UI daily of long-acting protaphane insulin respectively. Moreover, she was a smoker and carrier of heterozygous MTHFR mutation. Her body mass index was 23. She was genotyped for PTPN22 1858C>T polymorphism showing that she was not a carrier of the mutated T allele (12).

She was treated with corticosteroids (maximum dose 0.2 mg/kg daily) and methotrexate (up to 15 mg weekly, the maximum tolerated dose) until 2001, when infliximab was started at the dosage of 3 mg/kg every 7 weeks, achieving a good EULAR response (13). During infliximab therapy, anti-nuclear (ANA) and anti-double strand DNA antibody positivity was revealed, and chloroquine was started while methotrexate was discontinued due to persistent gastro-intestinal side effects. Moreover, lupus anticoagulant and anticardiolipin antibodies appeared for the first time, and anti-aggregant therapy was started. After seven years, the patient developed an erythematous facial rash and ANA and anti-dsDNA positivity was reconfirmed with a reduction of C3 and C4 complement proteins. At this time point, the Hb1Ac was 6.6%. Therefore, infliximab was discontinued due to drug-induced lupus. Adalimumab was started at a dose of 40 mg every other week, with an initial good EULAR response, but a subsequent loss of efficacy after 18 months was documented. Adalimumab was interrupted and sulphasalazine (2 gr/daily) in combination with rituximab was started (two 1000

mg doses two weeks apart). The patient was treated with 3 serial cycles of Rituximab 6 months apart each without reaching a good EULAR response. At this point, the Hb1Ac was 8.0%.

In 2012 CTLA-4 Ig was started at 10 mg/kg dosage using the induction scheme strategy (every 14 days for the first month, every 28 days afterwards). The patient was followed for 24 months reaching DAS remission after 6 months and the Hb1Ac was reduced to 6.1% (Fig. 1, Table I). Since RA diagnosis, low-dose corticosteroids were never interrupted. During CTLA-4 Ig treatment, no changes were made of the concomitant drugs and corticosteroid dose.

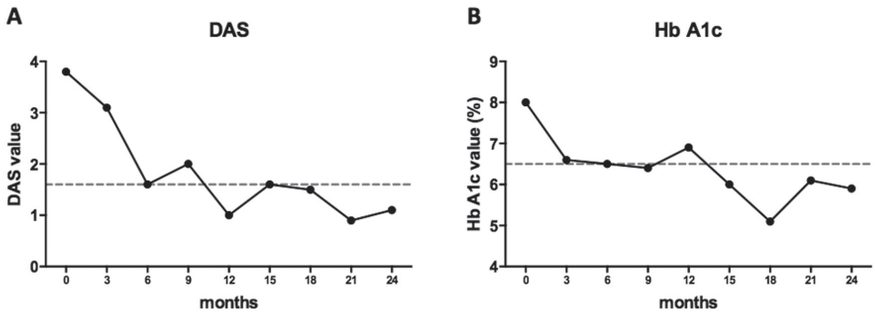

Fig. 1. DAS and HbA1c values overtime during CTLA-4 Ig treatment.
DAS: Disease activity score; HbA1c: Glycated haemoglobin; Broken line: reference value.

Table I. Laboratory and clinical parameters during CTLA-4 Ig treatment.

Time	ESR (mm/1 h)	CRP (mg/l)	HAQ	SDAI
Baseline	26	15.8	1.125	40.6
3th Month	17	4.3	0.375	22.4
6th Month	18	2.6	0.125	4.8
9th Month	21	5.7	0.125	9.6
12th Month	19	4.2	0.125	0.9
15th Month	14	3.2	0.125	4.3
18th Month	17	2.4	0.125	3.2
21st Month	13	3.7	0.125	5.4
24th Month	15	4.1	0.125	3.4

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein, HAQ: Health Assessment Questionnaire, SDAI: Simplified Disease Activity Index.

Discussion

We report the case of a patient with T1DM and RA with well-recognised poor prognostic factors, as RF and ACPA positivity, and erosive disease, that was successfully treated with abatacept obtaining RA disease and glycemic profile control.

Our clinical case suggests that besides traditional prognostic factors, comorbidities should also be considered when devising a therapeutic algorythm, since they decrease the chances of achieving remission (14).

Our patient was suffering from two autoimmune diseases, which may have a common genetic susceptibility, with RA being more prevalent in patients with coexisting autoimmune endocrinopathies (7). This possible common genetic susceptibility should be also taken into account in the therapeutic choices, although further studies are necessary to determine the role of this genetic background in RA pathogenesis.

After the failure of two anti-TNF drugs, according to EULAR recommendations (15), we chose a biological agent with a different mode of action, Rituximab, because of the positivity for RF and ACPA. After an initial moderate EULAR response (13), in repeated infusion cycles an absence of response was registered. Therefore, we started another biological drug, considering the patient comorbidities, also in order to optimize the glycemic control.

CTLA-4 Ig has been proven to be effective to halt or slow autoimmune beta cell destruction, in a trial with recently diagnosed T1DM patients (<100 days): this suggests that T-lymphocyte activation still occurs around the time of clinical diagnosis, even though the disease had probably began already several years before (9, 10).

CTLA-4 Ig has been described to be effective even in a patient suffering from RA and T2DM with an early improvement of insulin resistance by means of T cell suppression even in adipose tissue (11).

In our clinical case, the improvement in glycemic profile paralleled the RA disease control and was not explained by a reduction of corticosteroid dose or by changes in concomitant medications.

Moreover, our patient had an increased cardiovascular risk, suffering from both RA and T1DM as well as being smoker and carrier of MTHFR gene mutation. Based on this, obtaining a good RA disease control together with an improvement of glycemic profile, may ensure at least a partial reduction of cardiovascular risk (16).

In conclusion, we believe that the analysis of comorbidities should be included in the evaluation of the treatment choice in any RA patient. Since CTLA-4 Ig has proven to be effective in the early phases of T1DM, it could be used earlier in patients also suffering from RA, in order to exploit the window of opportunity of both diseases.

Further case series are welcomed to clarify whether RA carrying also T1DM may benefit from CTLA4 Ig intervention.

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