Using a modified Delphi process to establish clinical consensus for the diagnosis, risk assessment and abatacept treatment in patients with aggressive rheumatoid arthritis

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Abstract

Objective

We aimed to formulate consensus statements for the identification of patients with rheumatoid arthritis (RA) who may benefit most from abatacept treatment, in order to clear up points related to its use in rheumatology.

Methods

Two rounds of a modified Delphi process were conducted. In the first round, a board of experts defined a list of consensus statements based on data derived from a non-systematic review on the use of abatacept in adult RA patients. In the second round, clinicians with extensive experience in the treatment of RA were invited to express individually agreement on the statements, using a dedicated online platform. A face-to-face meeting of the board was held after round two. Consensus was defined as 75% agreement.

Results

In Delphi process round one, a board of 10 experts defined a list of 20 consensus statements on abatacept treatment. Then, a panel of 37 rheumatologists participated in round two. The majority of clinicians (75.7%) had 10 or more years of experience in the treatment of RA patients. Fifteen of the 20 statements reached the defined level of consensus.

Conclusion

Identified consensus statements may help clinicians to apply to routine-care settings results from clinical studies and clinical recommendations, providing a guide for the initiation of abatacept treatment in RA patients.

Key words

aggressive rheumatoid arthritis, consensus, abatacept, Delphi process

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory disease of synovial joints that carries a significant burden (1). The current paradigm for RA, according to the treat-to-target principle, associates intensive treatment early during the course of disease, with rigorous patient monitoring. The goal is achieving clinical remission or at least low disease activity within 6 months using standardised clinimetric evaluation (2, 3). To date, the RA treatment consists of synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs) (4).

Abatacept is a biologic agent that targets T-cell modulation via the co-stimulatory CD80/CD86:CD28 pathway (5). Its mechanism of action is unique among biologic agents, therefore, treatment is expected to achieve clinical efficacy in patients who are both naïve and inadequately responders to the other treatments with biologics (5). To date, several large-scale randomised controlled trials have established the efficacy of abatacept associated with methotrexate in RA patients (6-17). Moreover, recommendations for the management of RA released by the European League Against Rheumatism (EULAR) in 2013, advise the use of abatacept, as a potential choice for biological therapy for patients with RA showing an inadequate response to methotrexate (MTX) (2, 18). In the latest published recommendations licensed by the American Rheumatism Association (ACR), the role of abatacept as a possible first-line choice both in early and in longstanding disease has been confirmed (18).

The characteristics of abatacept – that is available in both subcutaneous (SC) and intravenous (IV) formulations (19) – together with absence of recommendations capable of identifying patient who may benefit most from abatacept treatment, represent an important challenge for clinicians, in patient's management. In order to clear up points related to the use of abatacept in the treatment of RA patients at different stage of disease, a group of Italian rheumatologists, among those that have extensive experience in the use of biological agents, reviewed the clinical evidence on abatacept and formulated consensus statements aimed to provide guidance on its use in routine clinical practice.

Materials and methods

Design and identification of experts

Delphi (20) is an indirect, anonymous, iterative process aimed at achieving consensus among experts, in consecutive stages of the process, based on the systematic feedback from the results of the previous rounds. A modified Delphi process (21) was used to generate and achieve consensus on abatacept treatment of aggressive RA. The definition of the consensus was determined before the analysis and was set at ≥75% agreement. Investigators were blinded to the results during analysis. Descriptive statistical analyses were performed using Epiinfo v. 3.5.4.

The process began with the identification of a board of experts in rheumatology; a research team of three methodologists and one specialist in RA developed a list of 10 experts from third-level clinical centres for the treatment of RA in Italy.

Delphi rounds

From September 2015 to February 2016, two Delphi rounds were conducted.

In the first round, the board of experts met for a full day meeting: at this time, data derived from a non-systematic literature review on the use of abatacept in adult RA patients were discussed and consensus statements were developed by research team and forwarded to the board, by e-mail, for definitive approval.

In the second round, using a practical approach, research team defined - with the help of the board - a list of clinicians from the main Italian RA clinical centres as well as from university departments, throughout the country. Research team considered clinicians who were highly trained and had extensive experience in the treatment of RA patient at different stage of disease. Every expert was invited to participate to the Delphi process by mailing. Using a dedicated online platform, consensus statements were presented to the clinicians, and they were invited to express individually agreement.

Table I. Rheumatologist panel characteristics, expressed as number of subjects (n) or percentage (%) for each category. Total subjects, n=37.

	n	%
Gender		
Female	20	54.1
Male	17	45.9
Practice type		
University-based hospital	18	48.6
Public or private hospital	19	51.4
Years of experience		
<10	9	24.3
10+	28	75.7

They rated each statement on a 5-point Likert-type scales indicating the 'agreement'. Free-text boxes were included for optional comments for each statement. The results were reviewed by the research team to determine whether comments could help in understanding similarities or differences in rating. Participants' characteristics, such as gender, years of experience and specialised field were collected. The Delphi platform was online for six weeks; reminders were sent to participants as appropriate.

All results from round two were shown to the board. Every statement was reviewed and opinions elicited from all experts. Free-text options were provided and qualitative data was gathered. Deadlocked items, that is, items for which ≥75% consensus was not achieved, were analysed. Plenary discussions of contentious statements were held.

Results

In Delphi process round one, a board of 10 experts defined 20 consensus statements focused on evidence for abatacept (8 statements) or indications aimed to provide support for abatacept initiation and choice of the administration of SC medication (12 statements). Indications on aspects with lower levels of evidence, such as disease risk assessment for the identification of RA patients who may have most benefit from abatacept treatment, were provided. For this purpose, RA patients were grouped into the following three categories: 1-recent-onset RA (<12 months) patients; 2- long-standing RA (>5 years) patients with poor response to MTX treatment; 3- RA patients with inadequate response to anti-TNF treatment.

In round two, identified consensus statements were introduced as an online questionnaire. A panel of 54 rheumatologists were asked to respond to the questionnaire. Of these, 37 agreed to participate in the Delphi process (response rate 69.8%) representing the most important Italian centres for the RA clinical care (Table I).

In general, 15 of the 20 statements reached the defined level of consensus as ≥75% of participants, indicated by a score of 4 (agree) or 5 (strongly agree). Five items did not reach the minimum level of agreement and neither were accepted or revalued.

The complete list of statements that reached the consensus is provided in Table II, statements are listed by identified RA categories.

The first set of statements refers to subjects with recent-onset RA. Statements I-II provide indications for risk assessment criteria, statements III-V provide indications for laboratory and instrumental assessment, whereas statement

Table II. Statements that reached the defined level of consensus.

I	In subjects with recent-onset (<12 months) rheumatoid arthritis (RA), the main prognostic factors of disease aggressiveness include: high number of swollen joints, persistent elevation of acute-phase reactant levels, presence of rheumatoid factor (RF) and/or anti-citrullinated peptide antibodies (ACPA) - especially if both at high titre – and early erosive disease.
II	In subjects with recent-onset RA, further prognostic factors of disease aggressiveness may include: power Doppler signal positivity in a high number of joints, systemic or extra-articular manifestations, tobacco smoking habit.
III	In subjects with recent-onset RA, laboratory tests that must be done at baseline include: complete blood count (CBC), liver and kidney function tests, urine test, glycemic and lipidic profile, erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) level, assays for ACPA/RF assay and blood protein electrophoresis.
IV	In subjects with recent-onset RA, it is essential to perform the following instrumental tests to evaluate baseline disease aggressiveness: hands, wrist, feet x-ray.
V	In subjects with recent-onset RA, it may be relevant to perform the following instrumental tests to evaluate baseline disease aggressiveness: power Doppler ultrasonography, magnetic resonance imaging (MRI) in selected cases
VI	In recent-onset RA not responsive to methotrexate (MTX), the combination of abatacept plus MTX is more effective than monotherapy with MTX.
VII	In recent-onset RA, the combination of abatacept plus MTX is more effective in subjects with the highest baseline ACPA concentrations compared to patients with lower concentrations
VIII	In subjects with long-standing RA (>5 years) and inadequate response to MTX who are candidates for biologic DMARD treatment, laboratory tests that must be done at baseline include: CBC, liver and kidney function tests, urine test, glycemic and lipidic profile, ESR/CRP level, ACPA/RF assay, blood protein electrophoresis, serum markers of Hepatitis B, antibody tests Hepatitis C virus, QuantiFERON-TB test, ANA (antinuclear antibodies) test, APL (antiphospholipid) antibodies testing (in case of anti-TNF therapy)
IX	In order to better characterise subjects with long-standing RA that meet eligibility criteria for biologic DMARD treatment, it is essential to perform the following instrumental tests: hands, wrist, feet x-ray.
X	In subjects with long-standing RA not responsive to MTX, the combination of abatacept plus MTX *vs*. MTX monotherapy, provides a better clinical response, with significantly lower rates of radiographic progression.
XI	Results from randomised controlled trials and observational studies indicate that in subjects with long-lasting RA, the combination of abatacept (subcutaneous or endovenous) plus MTX has an efficacy profile comparable to that of other biological agents.
XII	In subjects with long-standing RA and high titre of ACPA, the combination of abatacept plus MTX was particularly effective.
XIII	Results from randomised controlled trials and observational studies indicate that in subjects with RA not responsive to anti-TNF treatment, the combination of abatacept plus MTX demonstrated significant clinical and functional benefits.
XIV	In subjects with long-standing RA and high titre of ACPA, anti-TNF not responders, the combination of abatacept plus MTX was particularly effective.
XV	In the choice of subcutaneous administration route of abatacept the following factors must be considered: 1) factors related to the patient (such as patient preferences and/or patient adherence); 2) logistic factors of the RA centre (such as distance from the RA centre).

VI-VII summarise evidence on abatacept efficacy.

The next set of statements refers to subjects with long-standing RA and inadequate response to MTX who are candidates for biologic DMARD treatment. Statements VIII-IX provide indications on laboratory and instrumental assessment, while statement X-XII summarise evidence on abatacept efficacy.

Next, statements XIII-XIV summarise evidence on abatacept efficacy in subject with RA and inadequate or absent response to anti-TNF treatment. Finally, statement XV provides indications for the SC administration of abatacept.

Statements for which ≥75% consensus was not achieved were not deemed essential by the board of experts (Table III).

Table III. Statements for which ≥75% consensus was not achieved.

In selected patients with recent-onset RA, the combination of abatacept plus MTX from the beginning of treatment is more effective than monotherapy with MTX. Although at present this indication is not approved for use, abatacept plus MTX demonstrated robust efficacy with better long-term clinical, functional and radiological benefit compared with MTX alone, and a good safety profile.
In order to better characterise subjects with long-standing RA that meet eligibility criteria for biologic DMARD treatment, it may be relevant to perform the following instrumental tests: power Doppler ultrasonography, MR in selected cases
In RA subjects with inadequate response to anti-TNF therapy, who have to switch to another molecular target biological agent, laboratory tests that must be done at baseline include: CBC, liver and kidney function tests, glycaemic and lipid profile, ESR/CRP level/RF/other antibodies at baseline, ANA test, APL antibodies testing.
In order to better characterise subjects with inadequate response to anti-TNF therapy, who have to switch to another molecular target biological agent, it is essential to perform the following instrumental tests: hands, wrist, feet x-ray.
In order to better characterise subjects with inadequate response to anti-TNF therapy, who have to switch to another molecular target biological agent, it may be relevant to perform the following instrumental tests: Power Doppler ultrasonography, MRI in selected cases.

Discussion

The present study was aimed to provide statements useful in identifying aggressiveness of the disease in RA patients, who could therefore benefit from abatacept treatment. Three categories of subjects, recent-onset RA patients, long-standing RA patients with an inadequate response to MTX and RA patients with an inadequate response to anti-TNF treatment, were proposed.

Concerning patients with recent-onset RA, the updated EULAR recommendations (2) highlight the importance of diagnosing RA as early as possible in order to treat it appropriately. In patients with inadequate response to MTX, clinical practice guidelines recommend the use of biologic DMARDs in combination with MTX in all patients with poor prognostic factors (2, 18). According to the ACR recommendations, abatacept (as well as other biologics) could be used in particularly aggressive cases also from the beginning (18). Of note, abatacept has been recently approved in combination with MTX also in DMARD-naïve patients (22). Statements I and II specify prognostic factors of disease aggressiveness in recent-onset RA (*e.g.* high number of swollen joints, persistent elevation of acute-phase reactant levels), and provide shared clinical indications for the identification of factors related to a higher probability of radiographic progression and disability. Together with core negative prognostic factors (statement I), experts agreed in identifying additional factors of disease aggressiveness such as a positive ultrasound power Doppler signal for a high number of joints (23), systemic or extra-articular manifestations, tobacco smoking habit (statement II).

Laboratory and instrumental tests (statements III-IV), essential to evaluate baseline disease aggressiveness in recent-onset RA, also reached agreement. Furthermore, additional instrumental test such as power Doppler ultrasonography and magnetic resonance imaging (MRI) were identified (statement V). Regarding MRI, experts agreed that this imaging technique should be used in selected cases; this indication reflects the need to take into consideration economical restrictions. Statements VI and VII provide evidence-based indications on the use of abatacept plus MTX in patients not responsive to MTX. These statements aim to support clinicians' awareness of treatment-switching patterns recommended in recent-onset RA patients. In fact, results from clinical trials (9, 10) indicate that in recent-onset RA patients not responsive to MTX, the combination of abatacept plus MTX is more effective than MTX monotherapy and that subjects with the highest baseline anti-citrullinated peptide antibody (ACPA) concentrations have better clinical response with abatacept than patients with lower concentrations (8, 24).

In long-standing RA and inadequate response to MTX, agreement was reached on laboratory and instrumental tests (statements VIII-IX) essential at baseline in order to better characterise these patients. Concerning evidence-based indications for abatacept in this category of patients, experts agreed that abatacept plus MTX combination therapy provides a better clinical response than MTX monotherapy (statement X) and that the efficacy is comparable to that of other biological agents (statement XI), particularly in subjects with long-standing RA and high titre of ACPA (statement XII). These consensus statements are in line with the results of some clinical trials (8, 13, 14).

Concerning the last category of patients, experts agreed that abatacept plus MTX demonstrated marked clinical and functional benefits in RA patients not responsive to anti-TNF treatment (statement XIII) particularly in those with high ACPA titre (statement XIV). These consensus statements are in line with the results of recent clinical trials (12, 14).

With respect to the choice of the subcutaneous administration of abatacept, experts agreed on the importance of considering both factors related to the patient (such as patient preferences and/or patient adherence) and logistic factors related to the medical centre (the distance from the medical centre).

The goal of this modified Delphi process is to develop evidence-based consensus statements aimed to provide guidance on the use of abatacept in clinical practice. In this respect, in round one, 10 experts in the treatment of RA were identified (board) and a non-systematic review of the current literature regard-

ing the use of abatacept in adults RA patients was conducted. In the second round of Delphi process, trained clinicians operating in Italian Rheumatology centres were involved (panel).

We note that all participants to our Delphi process were Italian experts, and that the results reflect experiences and judgments of clinicians operating within the regional-based Italian health system. It is likely that identified issues are influenced by treatment patterns and health system pressures that arise within specific contexts in different Italian regions. Furthermore, in the present study no evaluation of safety was performed as this would have required more commitment from participants. To this regard, the Cochrane collaboration performed a network meta-analysis on the safety of the biologic agents (25). The study revealed that abatacept is associated with a significantly lower risk of serious adverse events compared to most other biologics and is significantly less likely than infliximab and tocilizumab to be associated with serious infections. In this regard, in the 2015 ACR recommendations update, abatacept is considered as the biologic DMARD of choice in case of previous serious infection (18). On the other hand, biologic agents are more effective in decreasing mortality compared to no therapy (26).

In conclusion, identified consensus statements may help clinicians to apply to routine-care settings results from clinical studies and clinical recommendations (27), providing a guide for the initiation of abatacept treatment in RA patients.

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