Updating the Italian Society for Rheumatology recommendations for biologic therapy in adult patients with inflammatory rheumatic diseases

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The advent of biological therapies has led to major changes in the treatment of different musculoskeletal inflammatory diseases, in particular rheumatoid arthritis (RA) and seronogative spondyloarthritis (SpA). After the approval of infliximab and etanercept in 1998-1999, a number of different drugs with similar or different mechanisms of action became available, expanding the possibilities of achieving a good control of signs and symptoms of disease in a sizeable number of patients, improving functional status and impeding or preventing the progression of joint damage as assessed by radiographs (1). However, a number of issues still remain unresolved: disease control is not adequate in a relevant percentage of patients, remission is achieved in less than one half of the patients and, finally, the possibility to achieve a long-standing, drug-free remission remains a wishful thinking in the majority of patients. Biological therapies also raised other important issues in that they are much more expensive and represent a major concern for payers because 1 month of a biologic drug may cost 100 times more than a year's supply of an older disease modifying anti-rheumatic drug (DMARD) such as methotrexate (MTX) or hydroxychloroquine (2). In addition, although biologic drugs have an adequate safety profile, relevant adverse events such as severe infections or tuberculosis reactivation can occasionally occur.

Thus, in an attempt to provide guidance regarding these questions and reduce variability in clinical practice, a number of national scientific societies have developed recommendations to optimise the treatment of RA and other inflammatory rheumatic diseases with biologic agents based on expert consensus and systematic review of research evidence, including the European League Against Rheumatisms (EULAR) recommendations for RA therapy by Smolen and colleagues published in the Annals of Rheumatic Diseases in May 2010 (3). However, even if the core set of recommendations is quite similar, many differences exist among different guidelines (4). Most countries suggest that RA patients must have failed to respond to at least one or more DMARDs (usually MTX), and have ongoing active disease, if they are to receive anti-TNF therapy; however, the definition of active disease differs widely. Different guidelines exert an important effect on access to anti-TNF treatment. One study, for example, found that less than 50% of patients receiving anti-TNF treatment in Denmark and Norway would be eligible for the same treatment in the UK (5). More recently, a comparison across 15 Countries found that the UK has the strictest guidelines and one of the lowest usage in the world (6).

One of the most relevant aspects of the new guidelines is that they incorporate the concept of "treating to target", a concept long established in the care of other chronic conditions such as diabetes mellitus and arterial hypertension. Implicit in such a concept is the idea that all patients can achieve the highest goals (remission or low disease activity) using available therapies and strictly controlling patients using standardized measurement of disease activity (7). Biologic treatments should be used in this optic and starting or stopping these drugs should be guided by strictly monitoring of disease activity.

The Italian Society for Rheumatology (Società Italiana di Reumatologia, SIR) has previously published (2006) a set of recommendations for the use of biologic therapies in RA (8). Since complete disease control is the main goal in treating RA today and this may require biologic treatment as well, it

was the objective of SIR to update the recommendations for the management of RA with biologic drugs in the clinical practice in order to help assure the optimal treatment of patients with RA and other chronic inflammatory rheumatic diseases. A committee of experts was therefore appointed in October 2008 with the remit of producing up to date, evidence-based, clinically relevant consensus recommendations for the use of biologic agents in inflammatory rheumatic diseases.

The committee was composed of expert rheumatologists, along with a number of fellows, who have been charged to participated in: (1) a critical appraisal of existing treatment guidelines; (2) a systematic review of scientific evidence to create an evidence report and draft recommendations; (3) a Delphi exercise to generate consensus recommendations; and (4) an exercise to grade the strength of recommendation.

A systematic literature search for existing recommendations for the use of biologic agents in IRDs published in any language between January 2006 and June 2010 was undertaken using MEDLINE, EMBASE, SCOPUS, CINAHL, AMED and the Science Citation Index. The search strategy consisted of two basic components: guidelines in any term (*e.g.* guidelines, recommendations, standards, algorism, or expert consensus, etc.) concerning biologic agents and inflammatory rheumatic diseases in any possible terms in the databases. In addition, Google (the first 100 hits) and seven Guideline Websites were searched, including the National Guideline Clearinghouse http://www.guidelines.gov/, Primary Care Clinical Practice Guidelines http://medicine.ucsf.edu/resources/guidelines/, the Guidelines International Network http://www.g-i-n.net/, Evidence Based Medicine Guidelines http://www.ebm-guidelines.com/, and the National Institute for Clinical Excellence http://www.nice.org.

The medical literature was examined for the 6 biologic agents on the market at that time: etanercept, infliximab, adalimumab, anakinra, abatacept and rituximab. The principles of inclusive search approach were to address indications and therapeutic response to biologic agents and to address the potential adverse events. Search for inflammatory rheumatic diseases included in particular RA and psoriatic arthritis (PsA), but also connective tissue diseases (CTD)s, vasculitis. Experts were invited to specify investigations in 4 main domains: 1) indications for use; 2) monitoring for side effects, including infections; 3) assessing the clinical response; 4) roles of cost and patient preferences in decision making.

Studies addressing the use of biologic agents were identified within each of the 4 prespecified domains. The literature search was limited to original research published in English language. The main focus was on SRs/MAs, RCTs/CTs, uncontrolled trials, cohort studies, case-control studies, cross-sectional studies and economic evaluations. Case reports were included only for non-RA and non-SpA diseases. Animal studies, non-clinical outcome studies, narrative review articles, commentaries and guidelines were excluded.

The efficacy of any treatment was determined by using the best available evidence. For example, when the efficacy of an intervention could be confirmed by category Ia evidence (MA/SR of RCTs), then studies lower in the evidence hierarchy such as individual RCTs (category Ib) were not reviewed. If there was more than one study in the same evidence level, the study with the best quality score was used. Information concerning side effects was obtained from both RCTs and observational studies. The full text of all articles was reviewed by 2 independent reviewers. If there was discordance on whether to include a study, it was resolved by a third reviewer.

The quality of SR/MAs was assessed using the Oxman and Guyatt checklist (9) and the quality of RCTs was evaluated using the Jadad method (10). Quality assessments were not undertaken for other types of study designs, such as cohort or case-control studies. For observational studies (case-control and cohort), we used the Newcastle-Ottawa Scale (NOS) (11).

At time of completion of the literature analysis done for these recommendations, six biological products were licensed in Italy. Three are anti-TNF drugs (infliximab, etanercept and adalimumab), one inhibitor of IL-1 (anakinra), one is a B-cell depleting drug (Rituximab) and one is an inhibitor of T-cell costimulation (Abatacept). With respect to the actual indication of regulatory agencies, anakinra and anti-TNF are indicated for treatment of active RA after DMARDs failure, while rituximab and abatacept may be used after failure of first-line biologic drugs. As for anakinra, which is still on the market in Italy, its efficacy profile seems to limit its use in RA, while it has been successfully used in the treatment of different inflammatory conditions (ie autoinflammatory diseases) (12).

In this supplemental issue of *Clinical and Experimental Rheumatology* the updated guidelines of SIR are reported with respect to efficacy and safety of biological agents in the treatment of RA and PsA as well as for their off-label use (13-16).

At the time of submission for publication, other biological agents came on the market. In particular, an inhibitor of IL6 receptor (tocilizumab), and 2 other anti-TNFs (golimumab and certolizumab). In the meantime, the European regulatory agency (EMA) also approved the use of Abatacept as first-line drug, after DMARD failure and this indication was accepted by the Italian Regulatory agency. The main features as of the new drugs are briefly described in the addendum.

Addendum

Tocilizumab

Tocilizumab (TCZ), is a humanised monoclonal antibody against the interleukin 6 receptor and has been approved in many countries for the treatment of moderate to severe RA. There are at least six fully published phase III studies supporting use of TCZ in the treatment of RA both in patients with insufficient response to TNF blockers and to DMARDs (17-22). TCZ has demonstrated significant clinical improvement in ACR response rate, individual ACR core set components, patient reported outcomes, DAS28 scores and radiographic progression. Signifi-

Table I. Categories of evidence and strength of recommendation.

Categories of evidence	
Ia	Evidence from meta-analysis of randomised controlled trials.
Ib	Evidence from at least one randomised controlled trial.
IIa	Evidence from at least one controlled study without randomisation.
IIb	Evidence from at least one other type of quasi-experimental study.
III	Evidence from non-experimental descriptive studies, such as comparitive studies, correlation studies and case control studies.
IV	Evidence from expert committees' reports or opinions and/or clinical experience of respected authorities
Strength of recommendation	
A	Directly based on category I evidence.
B	Directly based on category II evidence or extrapolated recommendation from category I evidence.
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence.
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence.

cant efficacy has been seen with both the 4 mg/kg and 8 mg/kg doses given every four weeks when compared with placebo. TCZ monotherapy was superior to MTX monotherapy in patients who had not had prior treatment failure (19).

TCZ has been approved as monotherapy and in combination with MTX for the treatment of moderate to severely active RA in patients who have either responded inadequately to, or were intolerant of, previous therapy with one or more DMARDs or TNF inhibitors. The recommended dose is 4 mg/kg given intravenously every 4 weeks. While showing efficacy as monotherapy and combination therapy with conventional DMARDs, the medication was generally well tolerated. Most of the adverse events were mild to moderate and comparable with placebo. However future studies should be considerably longer, with a larger population and include safety as a primary outcome. There is an increased risk of gastrointestinal perforation, and patients should seek medical attention for any new onset abdominal pain. Neutropenia, thrombocytopenia, elevated liver enzymes, and increased lipid parameters (LDL and total cholesterol) are all associated with TCZ use. Laboratory parameters should be monitored every 4–8 weeks. As other biologic agents TCZ should not be administered to those with active infections, those exposed to tuberculosis, or those with a history of serious or opportunistic infection. Other warnings include risk of malignancy, hypersensitivity reactions, demyelinating disorders, hepatic impairment and caution with live vaccinations.

Golimumab

Golimumab (GLM) is a human anti-TNF monoclonal antibody that was approved for use with MTX in adults with moderate to severe active RA, and, with or without MTX or other non-biologic DMARDs, in adults with active PsA or active ankilosing ppondylitis (AS). GLM is administered as a 50-mg subcutaneous injection once a month.

RCTs have shown GLM (plus MTX) efficacy in RA patients who have failed MTX (or other DMARDs) as well as in those with insufficient response to one or more anti-TNF blockers (23, 24). GLM also showed to be more effective than placebo in patients with PsA and AS (25, 26).

As with other TNF inhibitors, GLM should not be used (or used cautiously) in patients with active infection, heart failure, demyelinating disease, or a history of tuberculosis. Based on the finding that GLM was associated with exacerbation of asthma in a study in patients with severe asthma (27), patients with asthma should be monitored closely if they begin taking GLM.

Certolizumab

Certolizumab (CTZ) is a PEGylated humanised Fab' monoclonal antibody targeting TNF-alpha. It has been licenced for the treatment of moderate to severe active RA with or without MTX after failure of non-biologic DMARDs or anti-TNF drugs. It should be administered subcutaneously at the dosage of 400 mg every 2 weeks for the first month, and then 200 mg every 2 weeks.

In 2 randomised, phase III trials in patients with active RA despite previous MTX treatment, the combination of CTZ and a stable dosage of MTX was more effective than placebo plus MTX for improving the signs and symptoms of arthritis according to ACR criteria; radiographic progression was also inhibited 52 weeks after treatment initiation (28-29).

CTZ was generally well tolerated in combination with MTX or as monotherapy, with most adverse events being of mild-to-moderate intensity, Infections were the most frequently reported adverse events. As with other TNF inhibitors, CTZ should not be used (or used cautiously) in patients with active infection, heart failure, demyelinating disease, or a history of tuberculosis. Again, longer studies on a larger number of patients are needed to fully understand the safety profile of this agent.

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