Reconstructing the pyramid in rheumatoid arthritis. An urgent need

G.F. Ferraccioli¹, G. Valentini², G. Valesini³, S. Bombardieri⁴

¹Chair and Division of Rheumatology, DPMSC, Udine University; ²Chair and Division of Rheumatology, I University of Naples; ³Chair and Division of Rheumatology, University La Sapienza, Rome; ⁴Chair and Division of Rheumatology, University of Pisa, Italy.

Please address correspondence and reprint requests to: Prof. G.F. Ferraccioli, Chair and Division of Rheumatology, DPMSC, Policlinico Universitario, Piazza Santa Maria della Misericordia no. 1, 33100 Udine, Italy.

Received on May 10, 2001; accepted in revised form on September 20, 2001.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2001.

Rheumatoid arthritis (RA) is a crippling disease that affects 0.5 – 1% of the population and leads many patients to stop working within 10 years from the disease onset (1). Most people become disabled during the course of the disease (2, 3). The total direct cost per year is enormous. It has been estimated to range between $8,209 and $85,469 per patient in the US (1), and to be about $1 billion for the whole rheumatoid population in Italy (4). The indirect costs are much higher and when the direct and indirect costs and the loss of earning power are added together, the total burden has been calculated to be around $5 billion in Italy, a cost much higher than that of other chronic diseases such as multiple sclerosis (MS) or chronic obstructive pulmonary diseases (COPD).

In a disease with such a high burden, any new therapeutic option is viewed with much hope as a new possibility of improving pain, function and the quality of life and better controlling the disease (5). The appearance on the market of biologicals against TNF, which were shown to rapidly improve synovitis, even in poor responders to conventional treatments, had a tremendous impact on patients and on the rheumatological community (6). These agents have a high cost, however, and any health care system must face two main questions: (1) Which patients should receive these drugs? and (2) Is it possible to identify those patients with a poor prognosis – high joint damage, poor function, high disability – early on in the disease course?

These points are crucial in order to treat the right patient, i.e. the one with the most aggressive disease, and not to overtreat the wrong patient, i.e. the one with disease that will respond to conventional therapeutic approaches. The definition of the possible inclusion criteria is crucial because the most aggressive disease, the one leading patients to hospitalization, has been calculated to represent 43 – 75% of the direct costs of rheumatoid patients (7, 8).

While in oncology the neoplastic disease threatens the patient’s life, in rheumatology the patient’s worst outcome is not survival [although the life span is substantially reduced in patients with > 30 swollen joints at disease onset (9)], but a poor personal and social life, disability, perhaps multiple surgical interventions over the years, and loss of working capacity and earnings lasting years or decades. In these cases the cost to society is not very different between an oncology patient and a severely affected rheumatoid patient.

The cost of one year of treatment with a biological anti-TNF has been estimated to range between $7,000 - $25,000, while one year of treatment for breast cancer with taxanes has been estimated to range between $12,000 - $20,000. The conventional treatment for breast cancer ranges between $2,400 - $2,800 and in oncology the step-up approach is usual. In purely economic terms, the health care system should support those treatments offering the most efficacious drug, i.e. capable of reducing the loss of working capacity, disability, hospitalization and surgical interventions, once the disease has been defined to be resistant aggressive/progressive (10).

Defining severe rheumatoid disease

The typical patient with aggressive/progressive RA has a poor prognosis when treated with conventional DMARDs. Smolen in a recent editorial states that “two of the variables that best correlate with long term outcomes are the number of swollen joints and the level of C-reactive protein” (11). When analyzing the two parameters individually, the following points emerge. In his study on the sawtooth strategy of treatment, Mottonen (12) observed a poor outcome both in terms of lack of remission and the progression of radiological damage after an average follow-up period of 6.2 years in patients with >4 swollen joints (out of 66 examined) at entry. He also observed a poor outcome in patients with persistently positive rheumatoid factor (RF). Van Leeuwen (13) showed a strong correlation between the swollen joint count (SJC) (52 peripheral joints examined) and x-ray progression at 3 years, as well as between integrated C reactive protein values and x-ray progression. Several studies have demonstrated that positive RF at entry,
the presence of erosions at the moment the first diagnosis is made, and acute phase reactants can reliably predict the radiographic outcome for up to 5 years of follow-up (14).

Based on all of these data and the prognostic factors for disability (15), we may conclude that the following four parameters present at disease onset – RF positivity, at least one erosion, persistently high acute phase reactants (i.e. CRP > 20 mg/l), and a high number of swollen joints – may accurately predict patients who will have an aggressive and severe course. These are the patients that should be treated aggressively with the most effective and best tolerated DMARDs (i.e., methotrexate). These are the patients who tend to fare badly in terms of future outcome.

**Resistant RA**

Bingham and Emery have recently attempted to define an algorithm capable of identifying the patient who is truly resistant to MTX. They suggested that a 20% improvement in the ACR criteria or a poor to moderate response according to EULAR criteria should be the guideline to assess whether a conventional therapeutic strategy did or did not result in substantial benefits (10). We believe that, given the lack of data, the 20% ACR criteria or the EULAR criteria should be retained as guidelines for clinical trials, but in clinical practice we need a clear-cut definition of improvement that – according to the most recent studies – cannot be less than 50% (16). Therefore, given that once a 20% improvement has been reached this might be considered a positive response as recently stressed at the Nassau Meeting on Advances in Targeting Therapies (2001), rheumatologists should aim for a response of not less than 50%. Once a 3- to 4-month course with MTX does not improve the SWJ count and CRP by more than 50%, then a new strategy should be adopted.

In agreement with Bingham and Emery (10), a combination therapy should be tested as the next step (17-21). We have also shown that a step-up combination approach can control disease activity in a substantial percentage of patients (22).

If no major improvement (> 50%) is observed over the following 3 to 4 months, then the patient should be considered as having resistant-aggressive and progressive RA (RAP-RA). These should be considered candidates for anti-TNF or other biological response modifiers (BRMs such as CTLA 4 Ig; IL1 RA, etc.). In a previous consensus meeting (held in 2000) on TNF-blockers, it was agreed that patients going on to receive biologicals anti-TNF had to have active disease despite MTX (25 mg/w), defined as RA with a DAS28 > 3.2 or a combination of 5 or more swollen and tender joints plus high levels of acute phase reactants. We believe that these entry criteria only partially depict actual patients who are poorly responsive to DMARDs.

In fact, the feet are a very important issue in RA patients and the 28-joint count does not take into account the patient's feet. When using the ACR 66 joint count, as drawn from our study (23) and from Pincus (24), a swollen joint count exceeding 6-10, a persistently positive RF and the presence of new erosions after combination therapies might be more realistic cut-off levels to define the patient with RAP-RA, i.e. one needing therapy with anti-TNF- and/or other BRMs (25-27) (Fig. 1).

**Evidence-based medicine and long-term surveillance**

The concepts discussed in this editorial reflect the personal view of the authors as the result of a reappraisal of both their clinical experience and the most recent data presented in the literature. There is clearly an urgent need to modify and update the therapeutic pyramid for rheumatoid arthritis, given the demonstrated efficacy of new therapeutic strategies such as combination DMARDs, and the availability of newer chemical and biological agents.

In defining this therapeutic pyramid, however, we cannot simply rely on the support of evidence-based medicine, i.e. randomized controlled clinical trials. For instance no data are available on patients already treated with combination therapy. No data exist on whether the percentage of success is indeed lower than that reported in randomized controlled trials (RCT) or not. Due to their rigid criteria in terms of patient selection and treatment modalities, and their limited sample size, RCTs cannot possibly reflect the infinite variability observed at the bedside. Moreover, their limited duration is inadequate to properly evaluate the long-term effect of a given drug or combination of drugs on the natural history of the disease.

It is therefore imperative to carry out properly designed long-term observational studies aimed at monitoring both the effect of the drugs and the toxicity over time of all the protocols employed in RA. This approach has already been employed by single investigators and in multicentre studies and has yielded important information.

We believe that an important step in this direction would be, in cooperation with the regulatory health authorities, to identify and validate a core set of clinical and laboratory variables for long-term drug efficacy studies and to design a simple protocol that could be made available on the web.

At this point, in principle all the patients with RA around the world could be included in an international study, forming a vast pool that would be followed over time, although it would be advisable to initiate the study in a limited number of pivotal centres. A steering committee sponsored by the health authorities and scientific societies of the participating countries could be established with the objective of regularly analyzing the results of this follow-up study. We are convinced that there would be many advantages to a project of this nature. First of all, specialists would be left free to treat their patients at all times according to their experience and best judgement. Nevertheless, the use of standardized tools to monitor the disease would improve the quality of scientific communication and probably reduce the costs of redundant analyses. In addition, the possibility of participation by all rheumatologists around the world have an undoubtedly educational value, and reinforce the links between the individual specialist and tertiary centres. Finally,
analysis of the data that would be made available by this enormous database could help us to study and manage rarer complications and variants of the disease, and to identify with greater precision the safety and risks of the complex protocols that often must be employed. Last but not least, the realisation of this project would require only a limited budget.

In presenting this proposal to the scientific community, we are certainly aware of its enormous methodological and ethical implications, including the issue of the privacy of the individual patient, problems that obviously need to be solved before the project is launched.

At the same time we strongly feel that a study of this nature could constitute a formidable tool to meet the urgent need of our patients for the most effective, safe and affordable therapy that modern research can offer.

References