Possible discontinuation of therapies in inflammatory rheumatic diseases – as with initiation of therapies, a shared decision between patient and rheumatologist

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The guest editors are pleased to present the 15th annual Supplement concerning contemporary topics in rheumatic diseases. Previous Supplements in this series, available at the Journal website, include:

1999 – Combination DMARD therapy in rheumatoid arthritis
2000 – Bone mass in the rheumatic diseases
2001 – Controversies in COX-2 inhibitor therapy
2002 – Innovative therapies for spondyloarthritides
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2004 – Benefit/risk of new drugs for rheumatoid arthritis
2005 – Quantitative clinical assessment of rheumatic diseases
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2012 – Treat-to-target in rheumatoid arthritis: clinical and pharmacoeconomic considerations

The 2013 Supplement concerns "Possible discontinuation of therapies in inflammatory rheumatic diseases." This topic has long been important to rheumatologists and their patients, for example, historically, in decisions concerning possible discontinuation of gold salts and penicillamine in rheumatoid arthritis, cyclophosphamide in systemic lupus erythematosus (SLE), and other medications in various diseases. It has also been an area in which patient preference often influences tapering or stopping therapies.

Possible discontinuation of therapies has new importance at this time with availability of highly effective biological agents, which allow rheumatologists to treat more patients than previously to a target of low disease activity or remission (1). However, biological agents are more expensive than earlier medications and also may be associated with adverse events, though probably lesser than some traditional therapies for rheumatic diseases (1).

The Supplement presents a series of articles concerning the possible discontinuation of therapies in rheumatoid arthritis (RA), spondyloarthritides, psoriatic arthritis, SLE, vasculitides including giant cell arteritis, and juvenile arthritis. Ten points raised by articles in the supplement are summarised in this Introduction:

1) The diathesis of inflammation or disease activity in inflammatory diseases is based on a dysregulation, and dysregulatory diseases are currently "incurable."

Inflammatory rheumatic diseases result from an imbalance or dysregulation of "normal" body constituents, produced at a disproportionately high or low rate or level, resulting in a disturbance of homeostasis and consequent disease activity. This type of dysregulatory imbalance is seen in the etiology of many chronic diseases, such as hypertension or diabetes. Diseases resulting from dysregulation might be contrasted to diseases resulting from "abnormal" or external sources such as infections, allergies, or malignantly transformed cells, which may be "curable" by complete removal of microbes, allergens, or offending cells. However, diseases resulting from dysregulation of normal body constituents generally remain "incurable" at this time, other than occasional spontaneous remission. Even rheumatic diseases in which an inciting agent is known, such as reactive arthritis, remain "incurable." Further knowledge concerning the etiology of the dysregulation may be required for these diseases to become "curable."

2) Control of manifestations of a dysregulation or disease activity, generally with multiple medications, prevents organ damage, though usually requiring life-long treatment.

The primary problem for a patient with a dysregulatory disease often does not result from the dysregulation itself, such as elevated blood pressure, elevated glucose levels or painful joints. The most important consequences for the patient usually emerge from organ damage resulting from uncontrolled dysregulation, such as atherosclerosis, renal failure, or joint destruction. In most inflammatory rheumatic diseases, damage results from the sum of continuing inflammation over time. Control of disease activity to a low level or remission is associated with long-term reduction or prevention of long-term organ damage.

"Low disease activity" or "remission" may be defined differently in different diseases. In many cases, universally agreed-upon criteria currently are not available. Nonetheless, life-long medication usually is required to maintain a state of low disease activity or remission, as in other chronic dysregulatory diseases such as hypertension and diabetes.

3) The cancer chemotherapy model of "induction" therapy with multiple medications followed by "maintenance" with fewer medications may be valid for inflammatory rheumatic diseases.

A generally accepted principle in cancer chemotherapy is to initiate therapy with many agents as "induction," followed

by a "maintenance" phase with fewer agents. This approach is designed to gain as much efficacy as possible when therapy is begun, and then to maintain effectiveness subsequently, with a lower risk for adverse events. Such an approach in inflammatory rheumatic diseases could involve administration of a biologic agent to most patients for a short period of say, 6 months, followed by gradual withdrawal of the biologic therapy, as discussed in several articles in the Supplement.

4) Usually it is best to discontinue one medication at a time.

Most patients currently treated for inflammatory rheumatic diseases receive a combination of at least two medications, in contrast to earlier years when most patients were treated with glucocorticoid or DMARD monotherapy. In general, discontinuation of therapy should not involve all medications at one time, but rather only one medication at a time.

5) Usually, but not always, the biological agent should be the first to be discontinued.

Many experts suggest that the biological agent should be the first to be discontinued, based not only on costs, but also to minimise risk of potential adverse events. Biological therapies appear to be associated with lower risk of adverse events than historically used anti-rheumatic therapies such as gold salts or penicillamine. However, this risk is greater than for weekly low-dose methotrexate (even 25 mg per week is basically low dose) or prednisone at doses of less than 5 mg/day.

Although this approach generally is accepted in rheumatology, the dermatology literature suggests that biological therapy be continued and methotrexate should be used intermittently due to a greater risk of adverse events than seen with biological agents (see article by Ramirez-Fort *et al*. in this issue). It is possible that the adverse events profile of methotrexate differs in patients with RA *versus* psoriasis or psoriatic arthritis (2, 3). Furthermore, in certain individual RA patients or situations, *e.g*. planned pregnancy, methotrexate may be the first medication to be discontinued.

6) In general a discontinuation program must be gradual with a plan for all medications.

The discontinuation of small molecules or prednisone might proceed with a strategy to reduce a dose by, *e.g*. 1 mg of prednisone every month or two, or to administer a medication at twice the interval and then 3 times the interval prior to total withdrawal. This procedure provides evidence to the physician and patient that the ultimate goal of total withdrawal of that medication might be possible. If the patient cannot tolerate a longer interval between administrations, it would be inappropriate to attempt total discontinuation.

There may be a rationale for relatively abrupt discontinuation of biological agents, on the basis of immunogenicity associated with gradual withdrawal, although some experts suggest a similar gradual strategy for biologic agents. A long-term program of withdrawal of medication is desirable, often with a comprehensive plan for all medications. One or two agents might be retained indefinitely.

7) Consider strongly continuation of weekly low-dose methotrexate and low-dose glucocorticoids.

Weekly low-dose methotrexate is one of the safest medications in the modern pharmacopeia, in contrast to high doses of methotrexate as used in cancer therapy. Weekly low-dose methotrexate is anti-inflammatory, in contrast to cytotoxic or anti-metabolite properties of high-dose methotrexate (4, 5). Recent studies suggest that courses of methotrexate are continued five years after initiation by about 80% of patients with RA (6), a rate as high as almost any medication in clinical medicine. However, it is noted again that the dermatology literature suggests that biologic therapies appear safer than methotrexate, and recommends intermittent methotrexate and continuous biologic therapy (see article by Ramirez-Fort *et al*. in this Supplement).

Prednisone in doses of 5–10 mg/day has documented efficacy in patients with RA (7). Doses even less thsn 5 mg/day are efficacious (8) and do not affect the hypothalamic-pituitary-adrenal (HPA) axis (9). Therefore, prednisone in doses of ≤5 mg/day appears to be a safe therapy to continue on a long-term basis, in contrast to 10 or even 7.5 mg/day over long periods, in which suppression of the HPA axis is seen and potential for adverse events is increased (10). Some have suggested that a very low initial and maintenance dose of prednisone, generally in the range of 3 mg/day, may reduce or even prevent the likelihood of flares in patients who are in remission (11).

8) Assess response to therapy, and discontinuation of therapy, according to quantitative indices rather than narrative descriptions.

One of the most important developments in rheumatology over the past two decades has involved introduction of quantitative indices into clinical research and usual patient care. At this time, about 30% of American rheumatologists use a quantitative measure or index (12). It is likely that the percentage is greater in European settings, although it varies in different settings in different countries.

Quantitative assessment in usual care may help circumvent a traditional observation that "clinicians may all too easily spend years writing 'doing well' in the notes of a patient who has become progressively crippled before their eyes," published 30 years ago in *British Medical Journal* (13). It is as important to monitor discontinuation of therapy with quantitative data as it is to monitor a response to therapy quantitatively, as non-quantitative descriptions can be quite misleading to both doctors and patients.

9) Patients with earlier disease, who are in remission longer, and who have lower disease activity, are more likely to have a successful discontinuation of therapies, but wide ranges are seen for individual patients.

Clinical trials suggest that patients who have earlier disease, lower disease activity initially, and longer time in remission are more likely to discontinue therapy successfully than other patients (see sections in this Supplement on RA, spondyloarthritides, and psoriatic arthritis). However, the range of successful discontinuation may range from 20% to 80%,

explained by differences in patient populations and features of study design including agent, criteria for initiating discontinuation, criteria for successful discontinuation, period of observation, etc. The rates of "successful" discontinuation pertain to groups of patients, and many individual patients are exceptions to tendencies identified in groups.

Indeed, most information in the medical literature, including clinical trials, is reported in patient groups, and cannot identify optimal treatments and predict outcomes in each individual patient. Furthermore, different patients will interpret different levels of risk very differently. For example, a patient whose mother developed RA 30 years ago at age 50, was confined to a wheelchair at age 55, and died at age 60 might be far less willing to discontinue therapy than another patient with exactly the same measures of disease activity, whose neighbour was hospitalised for an infection secondary to biological therapy.

Each of these patients may be regarded as "correct," based on her or his individual assessment of risk and benefit to continue or discontinue therapy. Of course, patients often ask a physician to help them make a decision, but some patients may make a decision independently that differs from the doctor's choice. If the patient has a clear understanding of risks and benefits, and feels that the risks outweigh the benefits, that is reasonable. As discussed below, a shared decision between patient and doctor appears optimal (1).

10) The principle that "the treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist" always pertains to any decision concerning discontinuation of therapy in any disease.

The first principle of treat-to-target in RA (1) is that "The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist. Not only must the patient be informed of the therapeutic options and the reasons for recommending a particular therapeutic approach by weighing benefit and risk, but the patient should participate in the decision as to which treatment should be applied" (1).

A similar approach may be applied to treatment and discontinuation of medications in all rheumatic diseases. Information to identify patients who are at greater or lesser risk of relapse from discontinuation cannot predict the outcome in any individual patient with 100% accuracy, as noted above. Therefore, as in the treat-to-target recommendations, a shared decision between rheumatologist and patient is appropriate, based on data from clinical trials and clinical care, which patient and doctor interpret to provide the best risk/benefit evaluation for that individual patient.

We hope that the rheumatology community will find this Supplement of value for clinical care and further clinical research.

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