Review

Is there a rationale to using leflunomide in early rheumatoid arthritis ?

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ABSTRACT

The efficacy of leflunomide in the treatment of early rheumatoid arthritis (RA) patients might be attributed to the fact that it acts at several levels, including the anti-inflammatory and anti-destructive pathways. This is in addition to its inhibition of the L-dihydro-orotate dehydrogenase (DHOH) enzyme and pyrimidine de novo *synthesis which decreases cell proliferation and more specifically early activated CD4+ T cells, as well as monocyte interaction with T cells leading to cytokine and anticytokine production. Recent studies clearly indicate the rationale of an early administration of leflunomide in RA patients, particularly in the light of the results of previously reported clinical studies showing its rapid onset of action when compared to other DMARDs. The early efficacy and safety of leflunomide in patients with early RA is sustained over a long period, and the long-term safety profile of leflunomide does not seem to be different from that observed in phase III trials.*

Introduction

The therapeutic arsenal for RA has increased dramatically during the past decade and comprises both chemical compounds and new biological agents. The old concept of treatment of the symptoms has been extended to predicting the onset and severity of disease owing to novel genetic and immunoinflammatory markers. It is thus timely to identify and classify drugs known to interfere as early as possible in the progression of the disease before chronic processes are self-entertained and irreversible damage occurs. Considering the complex and varied nature of the mechanisms that lead to pain, inflammation, tissue destruction and lack of repair processes, as well the different cellular and humoral events, a wide therapeutic arsenal including a combination of DMARDs with our without biologics seem useful, not to say necessary in any stage of the disease.

Both activated immune/inflammatory cells and their products, at the level of the RAsynovial tissue, seem the principal targets for combined administration of effective antiproliferative (i.e. methotrexate, leflunomide) and biologic drugs (anti-TNF, IL-1Ra or anti-CD20). The administration of chemical drugs or biological agents also depends on the subtype of patients, the stage of the disease, or the type of clinical symptoms. We still have to understand which drug is appropriate in various stages of the disease. In the following review we will examine the role of leflunomide and the rationale of its administration in the early stages of the disease as well as the rationale of combining it with other therapeutic interventions, based on the most recent insights into the different mechanisms of action of leflunomide.

Outline of the physiopathology of RA

The physiopathological outcome of RA is inflammation, pain, tissue destruction and lack of repair processes affecting the articular and adjacent structures as well as occasionally other organs. Each of these cardinal manifestations is the result of individual or common humoral and cellular events (1-4). Strong evidences imply that pathogenesis of the disease depends on a given genetic HLA-DR4 background and on the hormonal balance (gonadal and adrenal) (5,6). The auto-antigens possibly involved in the etiology of RA are still not clearly identified, but the most recent data support the concept that modified peptides such as citrullinated peptides (anti-CCP) or degraded proteins of the host react with antigen-presenting cells (APC) and specific T cells –

mainly CD4+ of the Th1 type – to induce cytokine production and formation of auto-antibodies and immune complexes (7,8). The simplest model indicates that after homing to the synovial tissue the expansion of these T cells induces monocyte-macrophages, mainly by direct contact, to produce large amounts of IL-1 and TNF (9, 10). Macrophages are said to be important effectors of the immunoendocrinologic interactions in autoimmune rheumatic disease (11). IL-1 and TNF, in turn, induce endothelial activation, production of nitric oxide and chemokines, expression of adhesion molecules (inflammation), complement activation, production of prostanoids such as PGE2, production of kinines (pain), matrix metalloproteinases (tissue destruction) and RANKL (osteoclast maturation and bone resorption), inhibition of proteoglycan and collagen synthesis (lack of repair), at the same time as abnormal collagen synthesis (fibrosis) in inappropriate locations (12,13). Simultaneously, host defence mechanisms set in that are characterized by increased levels of cytokine inhibitors, i.e. interleukin-1 receptor antagonist (IL-1Ra), TNF soluble inhibitors and inhibitors of RANKL (OPG) (14). Unfortunately, the appearance of such inhibitory mechanisms are not sufficient to curtail the progression of the disease. IL-1, TNF and IL-6 act in synergy on hepatocytes by stimulating positive acute-phase proteins (i.e. CRP, SAA, anti-proteases such as α2-macroglobulin, α1-antitrypsin, but also in decreasing negative (reverse) acute-phase proteins (i.e. albumin, apolipoprotein A-1 and A-2). Of interest, HDL-Apo A-1 strongly inhibits the interaction between stimulated T cells and monocyte-macrophages and thus the production by the latter cells of TNF and IL-1 (15). Consequently, the decrease in HDL-apo A-1 levels induced by TNF, IL-1 and IL-6 unfortunately triggers a vicious circle by favouring the above-mentioned interaction (16). In contrast, the HDL-SAAcomplex can lead to cytokine production, chronic inflammation and amyloidosis. Recently, auto-antibodies to Apo A-I were discovered in patients suffering from various diseases (17, 18).

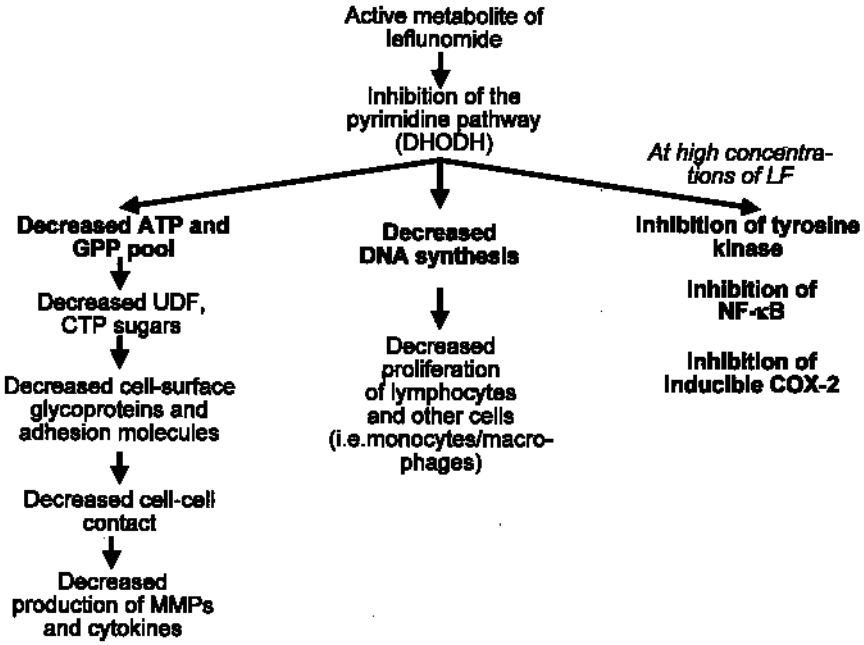

Fig. 1. Effects of leflunomide: some specific mechanisms.

Drugs affecting the physiopathology of RA

It is obvious that a single drug cannot counteract all of the different physiopathological processes of RA in every stage of the disease. By definition, a drug or biologic agent can exert a beneficial effect only if the target cell or mediator is present at a given time during the ongoing processes of the disease. Using a drug at an inappropriate time can only lead to side effects rather than improvement. Associating several drugs is justified only if they target different mechanisms. In accordance with this premise and subject to an association with other drugs, the administration of leflunomide is perfectly rational. To address all these questions it is necessary to analyse both classical and more recent modes of action of leflunomide.

Leflunomide's original mechanisms of action: Immunomodulatory and anti-proliferative effects (Fig. 1)

Leflunomide is a synthetic isoxazol derivative of low molecular weight (270 amino acids). Initially its effect as an antirheumatic drug was attributed to its ability to slow down progression through the cell cycle by inhibiting *de novo* synthesis of pyrimidine ribonucleotide (19-21). Unlike other cells, activated lymphocytes in RA require roughly an 8-fold increase in their levels of rUMP and other pyrimidine ribonucleotides in order to progress from G1 to S phase of the cell cycle and they have to resort to *de novo* synthesis of pyrimidine. It is the dependency of lymphocytes on the pyrimidine pathway that makes them very sensitive to leflunomide (22). Leflunomide is rapidly converted in the gastrointestinal tract and plasma into its active, open ring metabolite – malononitrilamide, A77 1726 - which conversion brings about the immunoregulatory activity (23). A77 1726 is tightly bound to plasma protein (>99%) and has a half-life ranging between 11 and 18 days.

The primary mechanisms of action of A77 1726 comprise immunomodulatory as well as anti-inflammatory effects (see Table I). The inhibition of tyrosine kinase activity decreases both expression and signalling of IL-2R, the reduction of IL-2 production, and enhances the levels of immunosuppressive cytokines TGFβ1 (transforming growth factor β1) (24). However, many of the known effects of the drug on signal transduction might be secondary results of a primary mode of action, i.e. inhibition of dihydroorotate dehydrogenase. By inhibiting the activation of nuclear factor kB (NF-kB), the drug also blocks inflammatory mechanisms

Table I. Classical mechanisms of action of leflunomide.

Lymphocyte proliferation: preventing cells from entering the DNAreplication phase (S phase) of the cell cycle
Inhibition of lymphocyte proliferation by blocking dihydroorotate dehydrogenase (DHODH), which enzme is crucial to the production of pyrimidine required for DNAsynthesis
Inhibition of lymphocyte proliferation association with the expansion of Tcells in rheumatoid arthritis
Inhibition of functional activity in human Tlymphocytes
Inhibition of the *de novo* biosynthesis of pyrimidine nucleotide in late G1 (growing)
T-cell-dependent B-cell formation of antibodies
Inhibition of nuclear factor kB (NF-kB) activation
Inhibition of tyrosine kinase associated with the initial stage of signal transduction in Go (resting)
Inhibition of MMPs, nitric oxide, PGE2, RANKLby monocytic-macrophage cells
Inhibition of IL-1, TNF, IL-6 by monocytic-macrophage cells
Inhibition of ICAM-1, VCAM-1 by monocytic-macrophage cells

such as the activation by TNF (25). Multiple studies have focussed on the inhibition of tyrosine kinase, but it appears that this mechanism is not the principal effect of A77 1726, owing to the weak correlation of the IC50 values with regard to lymphocyte proliferation versus the inhibition of tyrosine kinase activity.

On the strength of numerous studies it is assumed that one of the main actions of the drug is the inhibition of the *de novo* synthesis of pyrimidine. The addition of uridine generates a salvage pathway of pyrimidine, restoring the proliferative effect induced by A77 1726, but not when high concentrations of the drug are administered; presumably tyrosine kinase activity is inhibited at higher drug concentrations, regardless of the salvage pathway.

A77 17626 inhibits *de novo* biosynthesis of pyrimidine nucleotide at several sites. One of the most important effects of the drug is its effect on L-dihydroorotate dehydrogenase (DHODH). The rate-limiting step in the *de novo* synthesis of pyrimidines and progression of the cell cycle in different cell lines, mainly activated T lymphocytes but also other cells involved in the inflammatory reaction such as monocytes/macrophages, have proved to be affected. DHODH accumulates in human T lymphoblastoid cells treated with A77 1726, while exogenous orotate antagonises the effect of the drug. The non-competitive inhibition of DHODH occurs at drug concentrations similar to those resulting in immunoregulatory effects, i.e. 1 – 3 orders of magnitude less than needed for the inhibition of tyrosine kinases. Of interest, restriction of the *de novo* pyrimidine biosynthesis inhibits Th1 cell activation and promotes Th2 differentiation (26).

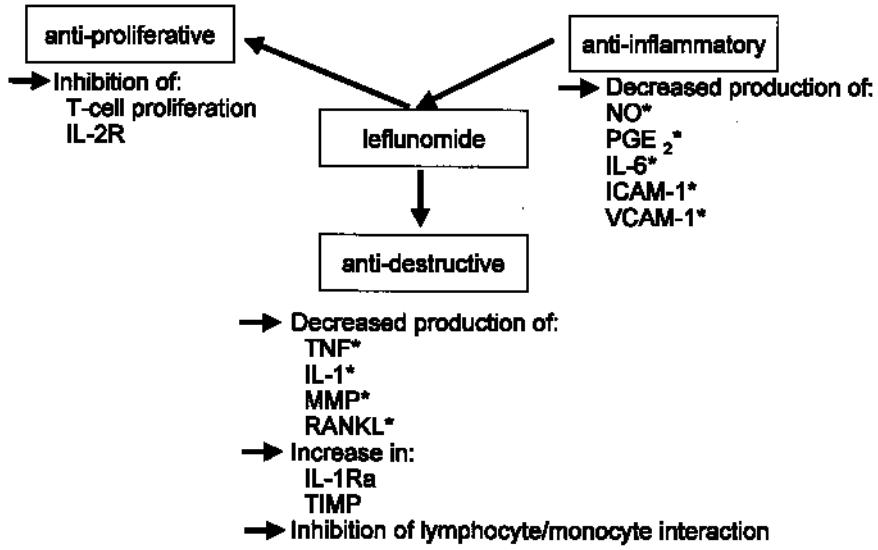

Fig. 2. Some major biological effects of leflunomide and possible synergism with anti-TNF* and IL-1Ra*.

Anti-inflammatory and anti-destructive actions of leflunomide (Fig. 2)

At the inflammatory site, inflammatory cells and cells of the native tissue are in close proximity in chronic inflammatory diseases. This implies that a possible mechanism of cellular communication is triggered by direct cell-cell contact and not only by soluble factors. A series of studies of cellular contact between T lymphocytes and synoviocytes have demonstrated that cell-cell contact induces the production of both matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinase-1 (TIMP-1) (27). In addition, direct contact leads to the upregulation of pro-inflammatory cytokines (IL-1 and TNF) and their respective inhibitors IL-1 receptor antagonist (IL-1Ra) and TNF soluble receptors (TNF-sR) (28). It has been postulated that an imbalance between levels of MMPand TIMPas well as cytokine and cytokine inhibitors may be conducive to matrix destruction, characteristic of chronic inflammation associated with RA. A77 1726 tends to inhibit preferentially pro-inflammatory (IL-1) and matrix destructive factors (MMPs) rather than anti-inflammatory factors (i.e. IL-1Ra) and MMP inhibitors (i.e. TIMP) (29, 30). This may be due to the fact that it inhibits the expression of cell adhesion molecules (CAMs) such as ICAM-1 and VCAM-1 (31). A77 1726 affords the depletion of ATP and GTP pools, thereby reducing ATP-dependent pools of UTP, UDP-Glu (urimidine diphosphoglucose) and CTP. Thus the subsequent expression of UDP sugars is inhibited, strongly impeding the glycosylation of

adhesion molecules. As a consequence transendothelial cell migration seems reduced, particularly of monocytes (32).

The active metabolite of leflunomide also inhibits the production of prostaglandin E2, MMP-1 and interleukin-6 in human fibroblast-like synoviocytes (33), it has anti-inflammatory effects on cultured synovial macrophages from RA patients and it decreases levels of IL-1, TNF, IL-6, nitric oxide, MMP-3 in activated human synovial tissue cultures (31, 34, 35), as well as chemokine expression (36). The active metabolite of leflunomide, A77 1726 also increases the production of IL-1 receptor antagonist in human synovial fibroblasts and articular chondrocytes (37).

Recently, leflunomide has been shown to inhibit osteoclastogenesis due to its interference with RANKL-stimulated induction of NFATc1 (38). These results confirm an extended influence and action of leflunomide on different cell types activated at the level of the inflammatory joint. Another recent study demonstrating the differential effects of leflunomide on IFNγ and IL-6 supports the hypothesis that leflunomide inhibits preferentially activated T cells (39).

Consequence in clinical trials and beneficial effect of early treatment by leflunomide

It is well recognized that irreversible joint damage and erosion occur soon after the onset of symptoms, often within the first two years, and therefore to control RA before joint damage sets in an early administration of DMARD is advisable. Among the different DMARDs currently used for treating RA, methotrexate and sulfasalazine are most frequently prescribed (40). Thus, a number of clinical trials have evaluated the efficacy of leflunomide in RA; most of them were multicenter randomized controlled trials (RCT) comparing leflunomide with placebo, methotrexate or sulfasalazine.

Leflunomide provides appropriately aggressive treatment in early RA and DMARD naïve patients

Data from two pivotal, placebo controlled phase III trials (MN301 and US 301) were analysed by Smolen *et al*. (41) to assess the efficacy of leflunomide compared to sulfasalazine and methotrexate in treating DMARD-naïve patients with rheumatoid arthritis disease duration of ≤ 2 years. A total of 233 patients who had a mean disease duration between 0.3 and 0.8 years and had no previously received DMARD treatment were included in this analysis. The mean age range of patients was 51.4–59.7 years and the majority were ACR functional class II or III. In study MN301, the 6-month ACR 50% response rates were 45.7% for leflunomide and 38.8% for sulfasalazine versus 22.2% for placebo ($p = 0.036$, leflunomide vs placebo). In study US301, at 12 month ACR50% response rate was 34.8% for leflunomide and 23.3% for methotrexate versus 0% for placebo ($p = 0.006$ leflunomide vs. placebo). In both trials CRP levels and radiographic progression were significantly reduced compared to placebo and were comparable with sulfasalazine and methotrexate.

Combe *et al*. (42) compared the efficacy of leflunomide in patients with previous methotrexate versus patients without previous methotrexate from the leflunomide 3012 study (43). A total of 272 methotrexate naïve patients and 127 methotrexate non-naïve patients were evaluated for efficacy at 6 months. The ACR 20, 50 and 70% response rates with leflunomide in patients with previous methotrexate were 48.9%, 20.6% and 7.7% respectively, whereas the ACR 20, 50 and 70 response rates with leflunomide in patients without previous methotrexate were 62.2%, 28.4% and 9.5% respectively. All ACR response rates were higher in methotrexate naïve patients compared to methotrexate non-naïve patients whatever leflunomide dose (10 or 20 mg daily).

Rapid onset of action which results in long term benefits

The efficacy of leflunomide was seen early, after 4 weeks of treatment, and was sustained for over 4 years in all ACR criteria components including mean CRP level, an accepted predictive marker of both severity and progression of disease (44, 45). Furthermore, based on dynamic gardolinium-enhanced magnetic resonance imaging (DEMRI), Reece *et al*. demonstrated that the improvement observed in synovial inflammation in terms of the initial rate of enhancement (IRE) was more significant in patients treated by leflunomide than in those treated with methotrexate over 4 months of therapy (46).

A systematic review of controlled phase II and III trials with leflunomide, including 2044 patients with RA, has been published (47). Leflunomide was shown to be efficacious and well tolerated in the treatment of active RAup to 2 years. In this meta-analysis, the pooled estimates of clinical efficacy showed leflunomide to be comparable to methotrexate or sulfasalazine in most of the clinical outcomes, except that leflunomide did better than sulfasalazine in improving the HAQ disability index at 6 months and the ACR20 response rate at 24 months. Interestingly, the large data base of RApatients from the leflunomide randomised phase III trials were reanalysed in order to assess if changes in the Health Assessment Questionnaire (HAQ) can measure the effectiveness of RA therapy (48). The patients had received 100 mg leflunomide (then 20 mg/day in 807 cases), methotrexate (15-20 mg/day in 669 cases), sulfasalazine (2 g/day in 132 cases) and placebo (in 209 cases). Changes occurred rapidly, and at month 1 were most pronounced with leflunomide. HAQ DI correlated closely with clinical response, as seen in changes in non-responders and ACR 20% and 50% responders and were consistent in patients receiving leflunomide across all 3 RCTprotocols (49-51) despite different baseline demographics, disease characteristics and HAQ scores in each trial. HAQ scores showed to be sensitive measures of effective DMARD therapy and may be especially useful early in the treatment process to assess patients' responses to DMARDs that show rapid onset of action. Furthermore, in leflunomide pivotal trials, improvements in physical function were sustained over 24 months of successful

treatment and reflect improvements in mental as well as physical domains of health related quality of life (52).

Regarding radiographic assessments of disease progression the results from the study by Strand *et al*. (49) and Sharp *et al*. (53) tended to favor leflunomide, while the results from the study of Emery *et al.* favored methotrexate (50), but there was no significant difference. For the comparaison between leflunomide and sulfasalazine at 24 months, leflunomide delayed joint erosions at a significant rate compared to SSZ (54). Van der Heijde *et al*. showed in a subset of patients who continued treatment longterm for up to 5.8 years that leflunomide treatment is associated with significantly reduced radiographic progression compared with both historical controls and pre-treatment estimated yearly progression rates (55). In all clinical trials radiographic progression was greater in patients who had erosions at baseline than in those who did not, showing again the interest of treating patients early in the course of the disease.

Long term benefits are confirmed in 214 patients (mean age 57 years) who were treated with leflunomide for a mean duration of 4.6 years (range 2.8 – 5.8 years); and of whom 32% had received no previous treatment with disease-modifying antirheumatic drugs (45). This study was the first current demonstration of sustained efficacy and safety of leflunomide in a subset of patients with RAwho received leflunomide therapy for up to 5 years. In addition, this study that reported the rapid onset of action of leflunomide relative to other DMARDs, further support that leflunomide has a valuable place in the treatment for early RA.

In real-life clinical practice leflunomide and methotrexate showed equal effectiveness as measured by time to treatment failure, defined as time to treatment discontinuation or to the addition of a second DMARD (56). In this analysis from the US National Databank for Rheumatic Diseases, 756 patients taking leflunomide and 675 taking methotrexate as part of their routine medical care were followed from 1998 through 2001. None of the 1431 patients had received either treatment previously. Patients were assessed at 6 month intervals for periods up to 36 months, the failure rate for patients taking leflunomide was 55.5 per 100 patient-years, and the median time to failure was 15 (95% CI 13, 17) months. For patients taking methotrexate the failure rate was 57.3 per 100 patient-years, and the median failure time was 14 (95% CI 12, 18) months. These differences were not statistically significant. A further study intended to determine the survival and clinical effectiveness of leflunomide compared with methotrexate and sulfasalazine for RA patients, evaluated a database of 1088 patients and 5141 patient years of DMARD treatment (2680 courses) from two academic hospitals (57). The median dose during the study increased from 10 to 15 mg methotrexate/week and from 1.5 to 2.0 g sulfasalazine/day. Matched survival analysis showed better retention rates for methotrexate [mean (SEM) survival 28 (1) months] than for leflunomide [20 (1) months; $p = 0.001$], whereas retention rates of sulfasalazine [23 (1) months] were similar to those of leflunomide (p = NS). Earlier cessation of treatment was prompted by adverse events (AEs, 3 months) rather than ineffectiveness (IE, 10 months; $p< 0.001$). Leflunomide and methotrexate were less likely to be stopped because of AEs than sulfasalazine. Retention of methotrexate was longer than that of leflunomide. Perhaps this is due to the fact that leflunomide has been administered strictly according to manufacturer's instructions and regulatory authority labels, and because toxicity appears to be increased only during the first few months after the beginning of the treatment. This calls for a re-evaluation of current loading dose requirements and dose increases in patients. In a more recent study, drug survival rates in patients with RA who started treatment by a biologic agent were compared to a control group of patients with a change in DMARD therapy after previous DMARD failure. RA patients were enrolled in the German biologics register between May 2001 and September 2003. Data were available for 511 patients treated with etanercept, 343 treated with infliximab, 70 treated with anakinra and 599 controls. Treatment continuation tended to be higher for patients treated with combinations of biologics and DMARDs than for those treated with infliximab or etanercept alone. After adjustment for baseline differences, the continuation rates were significantly higher in patients treated with biologics than in comparable control patients treated with leflunomide or leflunomide/methotrexate. However, the data on a combination of leflunomide or DMARDs need to be substantiated by long-term observations in the register and by other observational studies (58).

Safety of leflunomide in clinical trials and actual practice

Most importantly, clinical trials and post-marketing surveillance have shown that leflunomide is overall at least as safe as other DMARDs in RA. In the above mentioned meta-anlysisis of 6 randomized clinical trials with leflunomide totalling 2044 RA patients, the overall withdrawal rates and adverse events in the leflunomide group were not different from sulfasalazine or methotrexate (47).

In post-marketing surveillance to determine and compare the incidence of serious adverse events during treatment of RA with DMARD, a retrospective cohort study of a large US insurance claims database involving more than 40,000 RA patients was performed between September 1998 to December 2000 (59). Specific DMARD examined were leflunomide and methotrexate compared to other DMARDs including biological agents, all adverse effects reported were considered endpoints; leflunomide monotherapy had the lowest rate of hepatic events in the DMARD monotherapy groups. The rates of AEs in the leflunomide group, alone and combined with methotrexate, were generally lower than or comparable to the adverse effect rates seen with methotrexate and other DMARD agents. According to the authors of a recent review on the benefit and risk of leflunomide in RA(60), there is a lower risk of toxicity when leflunomide is used without a loading dose, at least when pres-

cribed in combination with methotrexate, and since relatively few cases of serious or opportunistic infection have been reported, it is reasonable to favor leflunomide over TNF inhibitors in patients with potential risk of infections. Recent work has updated the effectiveness and safety profile in RA and emphasizes the situation in actual practice as compared to clinical trials (61).

Rationale for treating early RAwith leflunomide based on new data

The efficacy of leflunomide in the treatment of early RApatients might be due to the fact that it acts at several levels, including the very beginning, of the immuno-inflammatory cascade.

(1) Indeed, by inhibiting DHOH enzyme and pyrimidines *de novo* synthesis, leflunomide decreases cell proliferation and more specifically early activated CD4+T cells which are more sensitive to pyrimidine depletion. This leads to a suppression of autoimmune T cell proliferation and thus first reduction of inflammation since most cells that infiltrate the RA synovium are CD4+ Tcells (21, 22).

(2) It decreases the functional activity of activated T cells. Exposure of T lymphocytes to leflunomide – but not to dexamethasone – favors the production by monocytic cells of interleukin-1 receptor antagonist (IL-1Ra) and the tissue inhibitors of metalloproteinase-1 (TIMP-1) over that of interleukin-1β and metalloproteinase (29, 30).

(3) Leflunomide inhibits the production of PGE2, MMP-1 and IL-6 in synoviocytes, when induced by IL-1 and TNF, and reduces the production of pro-inflammatory cytokines in monocyte-macrophages, TIMP-1 remaining unaffected (37). In a study on macrophages obtained from synovial tissue of RA patients, a progressive and significant time- and dose-dependent decrease in the number of macrophages positive for intracellular TNFα and IL-1β was observed after treatment with different doses of A77 1726 as compared to untreated cells. The extracellular concentration of TNFα was significantly decreased in media containing cultured macrophages at 24 h for all tested doses of A77 1726. At 24 h, a significant time- and dose-dependent decrease in the expression of ICAM-1 and COX-2 was observed in cultured macrophages after A77 1726 treatment (31). This inhibitory effect also reduces the activation of osteoclasts, involved markedly in joint damage. Other studies conducted simultaneously also show the inhibition of IL-1β, TNFα, nitric oxide and MMP-3 production in activated human synovial cell culture (35). A clinical study revealed a signficantly reduced number of macrophages associated with a significantly decreased expression of ICAM-1 and vascular adhesion molecule-1 (VCAM-1) as well as a decrease in levels of TNFα and IL-β in synovial tissue samples obtained from RA patients after 4 months of treatment with leflunomide (30).

(4) More recently, leflunomide has been found to inhibit osteoclastogenesis due to its interference with the receptor activation of NF-kappa B ligand-stimulated induction of nuclear factor of activated T cells (38). The direct effect of leflunomide on osteoclast differentiation was investigated using an *in vitro* culture system of bone marrow monocyte-macrophages stimulated with RANKL and macrophage colony-stimulating factor. The molecular mechanism of inhibition was analysed by genome-wide screening. *In vitro*, leflunomide proved to block *de novo* pyrimidine synthesis and RANKL-induced calcium signalling in osteoclast precursor cells; hence, the induction of nuclear factor of activated T cells c1 (NF-ATc1) was strongly inhibited. The inhibition of this pathway may be central to the action of leflunomide, since the inhibition was overcome by ectopic expression of NF-ATc1 in the precursor cells. This study suggests that the direct inhibitory action of leflunomide on osteoclast differentiation constitutes an important aspect in the reduction of bone destruction.

Rationale of combining leflunomide with other drugs or biologics

Considering the high failure rate of RA monotherapy and the multifactorial nature of the pathogenesis of RA, increasing emphasis is placed on combinations of therapeutic agents that act by inhibiting different pathophysiologic processes. Combining leflunomide with DMARDs proved beneficial to patients unresponsive to traditional monotherapy and, in particular, in the treatment of aggressive forms in early RA(60). This emphasizes the difference in modes of action between other DMARDs and leflunomide.

In most studies of disease-modifying antirheumatic drug therapy, in combination with either leflunomide or biological agents, patients are given an additional agent after failure of methotrexate treatment. A recent review of clinical studies shows leflunomide to be clinically efficacious and and well tolerated when added to sulfasalazine or methotrexate, whether in an initial or ongoing treatment of RA(62).

The rationale of combining leflunomide and anti-TNF or IL-1 receptor antagonist (IL-1Ra) is in theory based on complementary effects. Unlike anti-TNF and IL-1Ra, leflunomide mainly inhibits T-cell proliferation and tyrosine kinase activity and even cells proliferation of other activated cells involved in the articular inflammation (i.e. synovial macrophages or osteoclasts). Leflunomide acts on the pyrimidin pathway and DNA synthesis, also unlike TNF and IL-1Ra and therefore reduces the protein synthesis including the production of proinflammatory cytokines (i.e. TNF and IL-1). Leflunomide acts at the intracellular level, and the other two bind the TNF ligand or block the biological process at the receptor level. It remains to be seen if leflunomide also eschews – as does methotrexate – the emergence of human antibodies to TNF-α antibodies (63, 64).

Clinical trials combining leflunomide with biological agents are limited to a small number of open-label studies most of which with infliximab. Nevertheless, the combination of leflunomide and anti-TNF-α biological agents has been experimented widely in rheumatology centres throughout the world for the treatment of severe and/or refractory rheumatoid arthritis. In a retrospective study on leflunomide and infliximab case series showed comparable efficacy to the combination of methotrexate and infliximab (65). The combi-

nation is well tolerated when infliximab is added after leflunomide has been initiated. A recent study conducted in a cohort of 17 patients examined the safety of combining leflunomide and infliximab. Adverse events were not very different from those seen in patients on either treatment alone (66).

At present, the combination of methotrexate and anti-TNF is largely used, but its use has up to now been based on studies on a subpopulation of patients. In the light of those leflunomide combined to biologics agents preliminary reports, it may be worthwhile to investigate the effect of the combination in early arthritis. According to the opinion aired during an International Expert Panel Meeting held in Paris in 2003 and 2004, using a combination of leflunomide and biological agents was considered appropriate in patients with early disease (< 6 months) in whom the prognosis was poor in terms of rate of disease progression and risk factors. It was recommended to introduce biological agents in patients in whom treatment with leflunomide was already stabilised in order to optimise management of the emergence of potential side effects. Caution is advised, however, when using combination treatments and, therefore, the patient's safety should be carefully monitored (67).

Considering its mechanism of action, leflunomide could be particularly useful in combination therapy with methotrexate, considering that both drugs exert anti-proliferative effects at different levels. Unlike leflunomide, methotrexate – at the dosages used for RA therapy - appears to have little effect on T cell proliferation, but strongly inhibits cellular synthesis of polyamines and promotes adenosine release, which effects limit inflammation and joint destruction. Additionally, a recent in vitro study suggests that methotrexate promotes apoptosis of activated T cells, an action that would be complementary to the effect of leflunomide in limiting T cell proliferation. Testing of this combination in primate models was not possible because of significant differences in the metabolism, and thus in the pharmacokinetics, of leflunomide in humans and other primates. Twenty-three patients completed 1 year of treatment. No significant pharmacokinetic interactions between leflunomide and methotrexate were noted. This combination therapy was generally well tolerated clinically, with the exception of elevated levels of liver enzymes (68). The combination of methotrexate and leflunomide was found to have a strong therapeutic potential in RA. Later on, a randomized double-blind, placebo controlled trial was conducted to evaluate the efficacy and safety of leflunomide versus placebo when added to ongoing, stable-dose methotrexate in patients with persistently active RA. At 24 weeks 46.2% of the patients in the combination group and 19.5% of patients in the methotrexate plus placebo group met ACR20 criteria ($p<0.001$). Patients in the leflunomide group were more likely than those in the placebo group to experience elevated levels of liver aminotransferase enzymes. However, values normalized in all patients in the leflunomide group, in most cases with no adjustment of leflunomide dose (58.5%) or with one dose decrease (29.3%) (69). A 24 week extension to this study was conducted with the double-blind regarding initial randomization maintained. When patients receiving placebo had leflunomide added at Week 24, they achieved an ACR20 response rate at Week 48 of the same magnitude (58.3%) as that attained by patients originally randomized to leflunomide + methotrexate. This is especially interesting, as the patients who switched from placebo to leflunomide did so without a loading dose. Moreover, fewer adverse events including raised transaminase levels were reported in patients who were switched to leflunomide without a loading dose. However, although the reversibility of mild liver enzyme elevations in a clinical trial setting is reassuring, the potential for increased hepatic toxicity with the use of leflunomide and methotrexate combination should be recognized, confirming the need for regular liver enzyme monitoring (70). In this study only 10% of the patients had a disease duration of less than 2 years. Considering the complementary mode of action of leflunomide and methotrexate, the overall safety profile of the combination when appropriately monitored and the good clinical results in patients with established RAwarrant further trials in early RA(68 - 70).

Conclusions

The use of leflunomide in the treatment of early RApatients is supported by the fact that it acts at several levels of the inflammatory cascade showing antiproliferative and anti-inflammatory effects, together with a direct inhibitory effect on osteoclast differentiation. All these actions constitute an important aspect in the prevention of joint and bone deterioration.

Considering the antiproliferative activity exerted by leflunomide on activated T lymphocytes, the same mechanisms (alteration of the cell cycle progression) seem to interfere with the functions of other activated cells, i.e. monocyte/macrophages, strongly involved in the inflammatory reaction at the level of RAsynovial tissue. Therefore, a further anti-inflammatory activity exerted by leflunomide in RA seems to consist of the reduction of possible cell-cell interactions decreasing the intercellular adhesion molecule expression on synovial macrophages.

Clinical studies indicated that leflunomide is a safe and effective initial treatment of active RA, with a clinical benefit as regards to ACR responses, functional status and quality of life and radiographic progression of the disease maintained for up to 5 years without evidence of new or increased toxicity demonstrating that the early efficacy of leflunomide in patients with RAis sustained over a long period, and that the long-term safety profile of leflunomide is no different from that observed in phase III trials.

Leflunomide monotherapy provides appropriately aggressive treatment in early RA and DMARD naïve patients. Recent studies clearly indicate the rationale of an early administration of leflunomide in RA patients, particularly in the light of the results of the previously reported clinical studies showing its rapid onset of action when compared to other DMARDs. Finally, several recent trials have evaluated the effects

of combination therapy of leflunomide with other DMARDs and biologics. Although, it should be borne in mind that so far most of them have been of a preliminary nature, they have yielded results considered to be of great interest and warrant the use of such combinations therapy in patients with early RA.

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