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First Latin American position paper on the pharmacological treatment of rheumatoid arthritis

By the Latin American Rheumatology Associations of the Pan-American League of Associations for Rheumatology (PANLAR) and the Grupo Latinoamericano de Estudio de Artritis Reumatoide (GLADAR)

***Background*. Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that involves synovial joints, resulting in severe dysfunction or burden for individual patients, families and society. Latin American Rheumatology Associations have acknowledged its relevance and recognized multiple limitations for its diagnosis and treatment in Latin America and the Caribbean. This document underscores issues regarding the impact and relevance of this disease in these countries.**

***Objectives*. To develop a consensus document that may unify and guide the pharmacological management of RA in Latin America and the Caribbean.**

***Methods*. An Executive Committee appointed by the Epidemiology, Rheumatoid Arthritis and Radiology Committees of Pan-American League of Association for Rheumatology (PANLAR), held a meeting at Lisbon in May 2003. The goal was to establish a task force for the development of a Latin American consensus on the management of RA. Efforts focused on the problems encountered in the region regarding the availability of appropriate treatment for RA and the development of treatment guidelines for clinical practice. A secondary objective was the diffusion of the consensus conclusions and recommendations in participating countries.**

***Results*. Six major issues were identified for discussion by six working groups. All Latin American Rheumatology Associations registered in PANLAR were invited to participate in the consensus. PANLAR members were well-represented in each group. Coordinators identified essential literature to be reviewed, analysed, and electronically discussed before the consensus meeting.**

***Conclusions*. The consensus' results and recommendations of this effort to delineate RA management in Latin America are contained in this article, which has been reviewed by participant societies and authors during 2004/2005 and endorsed by PANLAR.**

KEY WORDS: Rheumatoid arthritis, Diagnosis, Therapy, Epidemiology, Latin America.

RA in the context of the overall socioeconomic and healthcare situation in Latin America and the Caribbean

Latin America and the Caribbean display complex demographic characteristics related to ethnic background, history of colonialism, and immigration patterns. The interaction of these factors has resulted in a mixed population that varies in each country, with a wide range of genetic expressions [1–3]. Nevertheless, key social problems, shared by most countries in the region, have been identified, including increasing poverty and its deleterious impact on society, growing unemployment and informal employment, deficiencies in public health, problems in education, newly impoverished populations, family deterioration, increasing crime, and the perverse cycle of socioeconomic exclusion. In fact, poverty affects half the population in the region, and inequity is perhaps more marked than in other regions of the world [4].

Rheumatic diseases in the context of health priorities

In developed countries, public-health efforts are currently aimed at increasing health-related quality of life. Healthcare disparities have been reduced through effective interventions, including mother and child care, as well as an improved management of infectious transmissible diseases. Thus, chronic diseases, which have great impact on health-related quality of life, are currently one of their priorities. On the other hand, Latin American and Caribbean countries show wide variations regarding major health objectives. At the same time, there is a need to address the problems and healthcare burdens posed by infectious diseases, mother–child health problems, and violence-related injuries, among others [5]. In many cases, this jeopardizes focusing public-health efforts on disabling diseases, such as RA.

RA has a significant impact on health-related quality of life, and is associated with increased healthcare costs and an increase in mortality when affected patients are compared with the general population [6]. These data underline the importance of considering early diagnosis and appropriate management of RA as a public-health priority in Latin American countries.

Early treatment of RA has been shown to reduce long-term disability effectively. This has the potential to save substantial costs to society [7]. Particularly, the development of newer therapeutic agents, such as tumour necrosis factor (TNF) antagonists, could help to modify the course and prognosis of the disease [8]. In such a context, the Chilean Ministry of Health has recently proposed that arthritis management should be considered as a major health objective for the current decade (2000–10). Health authorities have included arthritis, osteoarthritis and osteoporosis among the 'diseases that do not kill, but deteriorate quality of life by causing pain, limitation and suffering.' The goal for the year

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2010 is a 25% reduction in the number of patients with disabilities or chronic pain due to these conditions [9]. We hope that the use of newer diagnostic and therapeutic strategies will help to reduce the burden of these conditions on public health.

Epidemiology and demographic characteristics

Data on the incidence and prevalence of RA in the region are scarce. The incidence and clinical manifestations of RA have been shown to vary in many different geographical regions. In the white European population, the prevalence of RA is about 1%, with significantly lower rates in individuals of Asian and African ancestry. Moreover, recent figures in Spain and France show that the prevalence is around 0.5% [10]. Latin America and the Caribbean had a population of 531 113 893 inhabitants in the year 2003. Latin America has a younger population; it has been estimated that 70% of the population is older than 15 yrs. Some recent data on RA prevalence in Latin America are available. Between 1 January 1998, and 31 December 1999, Spindler *et al*. [11] found an overall prevalence rate of 0.2% for patients older than 15 yrs of age in Tucumán, a city in northwestern Argentina. More recently, in Brazil, Senna *et al*. [12], using the Community-Oriented Program for Control of Rheumatic Diseases (COPCORD) approach in a cross-sectional study of 3038 people, estimated a prevalence rate of 0.5% for RA for patients older than 16 yrs. Finally, using a similar approach, Cardiel and Rojas-Serrano [13] estimated a point prevalence rate of 0.3% for RA in Mexico City for patients older than 18 yrs old. Based on these data, a conservative prevalence rate of 0.4% could be estimated for Latin America as a whole; and taking into account a female:male ratio of 8:1, results in a total of 1 316 903 women and 164 612 men respectively, older than 15 yrs of age with RA throughout the entire region.

Ethnic heterogeneity is characteristic of the Latin American population. A multinational study by the Latin American Lupus Study Group (Grupo Latinoamericano de Estudio del Lupus, GLADEL) examined clinical and outcome differences for systemic lupus erythematosus (SLE), another connective tissue disease, and showed significant variations between different Latin American populations, including whites, mestizos (mixed racial background, specifically denoting the offspring of a Spaniard and an American Indian), and African-Latin American [14]. The findings of this study demonstrate the heterogeneity of the 'Hispanic' population. In addition, ethnic mixture and its epidemiological and clinical relevance are also demonstrated by the higher prevalence of RA among African-American and Afro-Caribbean individuals, when compared with black African populations [15].

Available information shows that, in Latin America, RA has its onset at an average of 40 yrs of age, approximately 10 yrs earlier than in white populations in the United States and Europe [16]. It is not known yet if this can be explained by special demographic features of the region's inhabitants or by true differences in age presentations. Women are more frequently affected than men, with a 7–8:1 ratio, well above US and European norms.

There are also differences in the clinical features of RA between Latin America and other regions of the world. In Chile, Massardo *et al*. [16] examined the expression of RA and its relation to the prevalence of genetic factors and found that extra-articular manifestations of the disease were fewer in Chilean patients. Overall, the severity of RA in this population, when compared with those described in other studies, was more in British patients, while Greek patients had milder disease. In Colombia, Anaya *et al*. [17] found that RA is less severe in terms of X-ray-documented lesions in African-Latin American individuals than in Colombian mestizo patients. In addition, the disease is not associated with HLA-DRB1 and DQB1 alleles. In Perú, Angulo *et al*. [18] identified an association of RA with HLA-DRB1*0404. Also, Ruiz-Morales *et al*. [19] associated the susceptibility for developing RA with the HLA-DRB1 allele encoding the shared epitope in Mexican patients.

On the other hand, Citera *et al*. [20] examined the influence of HLA-DR alleles on RA susceptibility and severity in Argentinean patients. Their results coincided with those of studies on Caucasian populations, and differed from those described for other Latin American populations. Again, these data reflect the impact of genetic variability on RA characteristics in Latin America.

Quality of life, disability and pharmaco-economics

A highly relevant issue in RA is its impact on the patients' quality of life. Early diagnosis and treatment are positively correlated with this impact. Unfortunately, in a study by Massardo *et al*. [16] the time interval between the onset of disease and initial evaluation was 2–6 yrs. Most manual workers stop active labour 2 yrs after disease onset, increasing indirect disease-related costs and affecting patients' quality of life. Cadena *et al*. [21] showed that the quality of life is significantly reduced in RA patients living in Medellín, Colombia. Disability-associated lost years (DALY) of healthy life because of RA in Chile were estimated at 21 663 for the year 1993 [22]. The same year, RA ranked 14 among the first 15 leading causes of lost years of healthy life due to disability in Chile.

Disease-related costs are a major issue, particularly in the context of limited healthcare resources, common to all Latin America and the Caribbean. The economic impact of RA has been examined in various studies. A cost-appraisal study made in Caracas, Venezuela, by Martinez [23] showed that, in 1997, the annual per capita cost in US dollars for a patient with RA was US$ 698.07; and by 2002, this cost had risen to US$ 3 493.80. In 1997, Ariza-Ariza *et al*. [24] examined the direct costs of medical care for RA patients in a tertiary centre in Mexico City, and found that it ranged from US$ 228–2 661 per year, depending on the rate of activity and the severity of the disease, as well as the socioeconomic level of the patient. Notably, by that time the minimum wage in Mexico was US$ 90 per month. More recently, Audisio *et al*. [25] reported that half-year direct costs from RA in Argentina were very high (US$ 677), especially considering the monthly mean home income (US$ 426) of patients with the disease.

Special concerns in Latin America

Qualified manpower availability to treat RA is insufficient

The World Health Organization (WHO) has recommended that there should be at least one rheumatologist per 100 000 people. Thus, in Latin America there is an estimated need for 5000 specialists. Currently, Pan-American League of Associations for Rheumatology (PANLAR) has 2000 active members, not all of them rheumatologists. The real number cannot be accurately determined since some practicing rheumatologists are not affiliated with local societies. This number is well short of WHO recommendations. Therefore, RA remains either unrecognized or inadequately treated in a large proportion of affected individuals.

Participants in the consensus meeting of PANLAR agreed that improving RA diagnosis and treatment through appropriate, continued medical education of primary care physicians is critical for enhancing the quality of care delivered to individuals with disease. They noted that the patients are usually referred to a rheumatologist at a late stage, between 2–6 yrs after the onset of symptoms. This experience is highly alarming, since the presence of hand synovitis for 6 weeks or more should raise a strong clinical suspicion of RA.

In addition, certain cultural beliefs, such as 'RA is a disease of the elderly' or 'RA therapy does not work, and may do more harm than good,' also hinder appropriate diagnosis and treatment of the disease. Educational programmes and campaigns aimed at increasing community awareness of the importance of RA could

help to change these misguided beliefs and attitudes. Unfortunately, in many countries of the region, RA is not recognized as a major public-health problem. Special emphasis is needed on educating medical personnel, regional authorities and RA patients. This was part of a second meeting that was held in Reñaca Chile in 3–4 October 2005 in which recommendations for education were developed and will be disseminated in the region.

Deficient drug availability and access to therapy

The pharmacological armamentarium for the treatment of RA available in Latin America and the Caribbean is similar to those of developed nations. Distribution and use of such agents strongly depend on commercial market forces and the interests of manufacturing companies. Drugs used in the management of RA as currently recommended are highly expensive. In a study by Audisio *et al*., [25] medication costs accounted for 89% of the estimated mean half-year cost of RA therapy in Argentina. In addition, healthcare for RA competes for funding with global poverty, poor education and other basic health problems. In this scenario, access to internationally recommended therapy for most people suffering from RA is highly problematic. The majority of patients in the region have limited access to medications, rehabilitation and orthopaedic therapies, all of which are highly recommended by the American College of Rheumatology (ACR) in its 2002 treatment guidelines [26].

Inadequate medical records and information

Another strategy needed for enhancing the recognition of RA in Latin America is to improve information and recording systems on the use of resources and the economic consequences of the disease. The impact of the disease on the general population should be underscored by developing reliable epidemiological data on the number of RA patients treated every year *vs* the estimated number in the total population. The use of standardized data based on the International Classification of Diseases (ICD-10) code in medical records and charts is of utmost importance in achieving this goal.

Moreover, clinical charts should include relevant information on demographic and occupational issues. The indirect economic impact of RA could be highlighted if its impact were to be measured in terms of work absenteeism, medical leave, work licenses, early retirements, layoffs, and use of public and private social support resources and programmes. The diagnosis of RA among the causes of death should also be emphasized.

Unrecognized morbidity and mortality of RA

The public and healthcare administration officials are unaware that RA is indeed a potentially catastrophic disease. Sufficient funding and reimbursement to treat at least the most severe cases are critical.

Disease severity

RA is a chronic disease that produces pain and disability, progressive joint destruction, and premature death [27]. There is now compelling evidence that the irreversible joint damage in RA occurs early in the course of the disease (often most rapidly during the first 6–12 months of disease); and therefore, the conservative approach of 'wait and watch' is today absolutely unacceptable [28, 29]. Within the first 2 yrs following onset, 50–70% of patients will have developed radiologically evident erosions [30].

RA is also associated with increased mortality rates, when affected individuals are compared with the general population [31]. In a recent population-based study made in Finland, RA patients had an increased risk of death from various causes, including urogenital, gastrointestinal, respiratory and cardiovascular diseases *vs* the general population [6]. Increased morbidity and mortality in these patients can be attributed to different factors, including treatment-related complications, increased risk of infection, and the presence of systemic extra-articular disease manifestations [31]. Turesson *et al*. [32] found that the greatest increase in mortality in RA patients occurred in those with severe extra-articular manifestations, suggesting that such manifestations are the major predictors of mortality in patients with RA. Two studies from the Mayo Clinic show that RA patients have twice the risk of developing congestive heart failure and that the presence of systemic inflammation is associated with a statistically significant additional risk for cardiovascular death among such patients *vs* the general population [33, 34]. These data also underline the importance of early diagnosis and appropriate treatment.

Early and aggressive treatment with traditional and biological disease-modifying anti-rheumatic drugs (DMARDs) has been shown to improve the prognosis of disability and inhibit radiographic progression [35–38]. However, certain issues affect the implementation of early and effective treatment, including the lack of definite diagnosis criteria in early RA, delay in qualified medical attention, and difficulty in identifying patients likely to develop persistent disease or with risk factors for severe or erosive disease [27, 37, 39].

Classification criteria developed by the ACR show a sensitivity of only 81% when applied to patients with RA for < 1 yr [39]. Other studies show that these criteria failed to discriminate patients with clinically diagnosed RA and also to identify patients who would develop persistent, disabling and destructive disease [40].

In many cases, delay between the onset of symptoms and initiation of therapy is a result of a delay in the referral of patients to a rheumatologist [27, 29]. Studies in the US and the UK demonstrated delays from 8 weeks to 4 months in the referral to a specialist, with only 20% of patients with symmetric polyarthritis and positive rheumatoid factor (RF+) being diagnosed with RA within 2 months of disease onset [27, 29]. Patients with suspected RA must be referred quickly to a rheumatologist for early diagnosis and treatment to obtain the best outcomes.

Early identification of patients likely to develop persistent disease or those with risk factors for severe disease is extremely important, since they might benefit most from rapid and intensive therapy. The incidence of persistent disease varies depending on the type of study. Population-based studies show an incidence of 27–28%; and, those performed in the context of early arthritis clinics reported even higher figures (45–49%) [27, 35]. Likewise, prognosis and remission rates differ considerably among patients with recent-onset polyarthritis, especially if they are seronegative [30]. Remission rates in these patients can be as high as 75% [30].

Prognostic factors

Prognostic factors for persistent and severe disease in patients with recent-onset polyarthritis and established RA are reviewed in the next several paragraphs. It is important to underscore that a great majority of these factors are clinical and easily measurable, and should be routinely screened for in the care of these patients. They are classified as demographic, disease-related and comorbidities (Table 1).

Demographics

Various studies have identified female gender, early age of onset of the disease, and low educational and socioeconomic levels as factors associated with poor prognosis [26, 41–43]. The independent value of each of these prognostic factors must be evaluated

Table 1. Factors associated with a poor prognosis in RA

Demographic variables
Female gender
Young age
Low level of formal education
Low socioeconomic level
Disease-related variables
Diagnostic
Disease activity
Functional capability
Radiographic damage
Extra-articular involvement
Positive rheumatoid factor
Diagnostic
Genetics
Comorbidity

along with factors inherent to the disease. Factors of particular relevance in Latin America are low educational and socioeconomic levels.

Disease-related factors

These factors can be further stratified into diagnostic, disease activity, loss of functional abilities, radiographic joint damage, extra-articular manifestations, and serologic and genetic factors (Table 1).

Diagnostic factors

Delayed diagnosis, prolonged interval between the onset of symptoms and the beginning of treatment, and longer disease duration, all carry poor prognoses, along with an increased likelihood for the development of radiographically evident lesions and disability [27–29].

Disease activity

Many studies have demonstrated that disease activity is an important predictor of radiographic damage and disability [42–47]. Disease-activity markers that must be carefully considered are swollen joints (>20) [26, 42–44], increased erythrocyte sedimentation rate (ESR), or high concentrations of C-reactive protein (CRP) [26, 42, 43]. A disease activity scale combining different variables has been developed recently and its usefulness in the evaluation of patients and their responses to treatment has been demonstrated [45]. A Disease Activity Score 28 (DAS28) greater than 5.1 means high disease activity, whereas a DAS28 less than 3.2 indicates low disease activity. Remission is indicated by a DAS28 lower than 2.6 [48].

Loss of functional abilities

Poor functional capacity at disease onset, measured either by Steinbrocker's classification [47] or by the Health Assessment Questionnaire (HAQ) [41], is also a marker of poor prognoses.

Radiological evidence of joint damage

Radiological examination of hands and feet should be performed for all patients with RA, since it allows a baseline evaluation for the subsequent assessment of disease progression and response to therapy [26]. Radiological evidence of premature damage in hands and feet is a measure of poor prognoses, not only for radiological progression but also for disability [44]. Newer, more sensitive methods for the detection of radiological damage, such as ultrasonography [49, 50] and magnetic resonance imaging [50, 51], have been examined during the past few years.

Extra-articular manifestations

Extra-articular manifestations such as rheumatoid nodules, Sjögren's syndrome, episcleritis, scleritis, interstitial lung involvement, pericardial involvement, systemic vasculitis and Felty's syndrome are indicative of worse prognoses [26].

Serologic factors

RF+ RA patients, especially those with high titres, have worse prognoses than seronegative RA patients [26, 41–46]. Other serologic findings such as elevated serum agalactosylated IgG [44] and, in particular, the presence of antibodies against cyclic-citrulinated peptides, have been associated with poorer prognoses, equivalent to RF positivity [52–54]. However, because of their cost, lack of conclusive evidence, and relative usefulness in Latin America, the use of antibodies against cyclic-citrulinated peptides as prognostic markers are not recommended at this time.

Genetic factors

The presence of HLA-DR4 and a shared epitope has been correlated with increased radiographic disease progression. Several studies in Latin America have examined this association, with inconsistent results [20, 55–58]. For example, Angulo *et al.* [18] did not find the combination HLA-DRB1*0401/0404 in any of the 52 patients examined in Peru. This is likely to be a result of the genetic variations in the Latin American and Caribbean population as discussed earlier in this article. For this reason, genotyping for the prognostic evaluation of RA is not recommended in Latin America at this stage in the development of RA treatment and management guidelines.

Comorbidities

Recent evidence has established that, in spite of the advances in RA diagnosis, evaluation and therapy, RA-associated mortality has not decreased during the past decades [59].

In addition to disability and radiographic damage, mortality should be considered an important endpoint in RA. In this regard, comorbidities (e.g. heart disease, hypertension, diabetes, and others) should be evaluated at disease onset [59–64]. Special attention should also be given to atherosclerosis and cardiovascular disease in these patients, especially with respect to their relation to disease activity and treatment. It has been shown that patients with RA have altered lipid profiles, including high serum Lp(a) lipoprotein, lower high density lipoprotein (HDL)-C, and higher triglyceride concentrations [65]. In these patients, disease activity, sex and menopausal status affect the lipid profiles [66]. Other studies have not shown the same findings, although higher homocysteine concentrations were found in patients with RA compared with healthy controls; higher homocysteine concentrations were associated with higher cardiovascular risk [61]. It has been suggested that the higher risk for cardiovascular disease seen in RA patients could be associated not only with traditional risk factors, but also with endothelial cells dysfunction and inflammation related with the autoimmune disease process [67, 68].

In summary, all patients with RA should be treated early with DMARDs. Early referral of individuals with suspected RA to rheumatologists is important to improve prognoses and select therapies [60].

Patients with poorer prognoses should be treated more aggressively with higher doses and/or drug combinations.

Table 2. Suggested outcome measures in RA

In the outpatient clinic
Every visit
Tender and swollen joint counts (at least 28 joints)
Pain
Disability (Short HAQ)
Patient's and physician's global evaluations of disease activity
Acute phase reactant values (ESR; PCR)
Disease Activity Score 28 or 44
Laboratory evaluations to monitor drug toxicity
Optional
Quality of life instruments (SF-36, FACIT-F, HUI)
Annual evaluation
X-rays (at the beginning and every year. We suggest hands, feet and cervical spine)
In clinical trials
Same as aforesaid but more comprehensive evaluations are needed for joint counts. Use of complete HAQ and quality of life instruments tends to be a rule.

It should be kept in mind that some patients are more likely not to respond to standard therapies.

Outcome measures

RA patients should be properly evaluated in clinical settings and clinical trials. A core set of outcome measures to be used in clinical trials has been proposed and accepted. These measures include patient's and physician's global evaluations, swollen and tender joint counts, pain, function and acute phase reactants, as well as X-ray evaluations [69]. Two sets of therapeutic response criteria proposed by the ACR and the European League against Rheumatism (EULAR) are also available; both have been fully validated and are widely accepted by rheumatologists [70, 71].

We propose that all RA patients be periodically evaluated in clinics with a minimum set of clinical, functional, laboratory and radiological studies as depicted in Table 2. This will provide a good opportunity to establish large data sets that can be used for research purposes and compare different groups of patients, and to determine when a patient should be treated more aggressively.

Clinicians in this meeting agreed that therapeutic decisions should be based on disease-activity indices. The final goal is to reach remission (DAS28 < 2.6), but low disease activity is also a realistic and reachable clinical outcome (DAS28 < 3.2). We consider that a DAS28 score ≥ 3.2 following treatment should be considered a therapeutic failure, in need of alternate therapy or regimen adjustment.

Treatment

Since disease activity can be the most significant factor responsible for joint damage, disability and radiographic progression, the main objective of therapy is to achieve clinical remission and, when this is not possible, to minimize disease activity. Treatment should be aimed at controlling inflammation, minimizing joint destruction and radiographic progression while preserving functional and work capabilities, and improving quality of life. RA treatment should include an adequate balance of physical therapy, medications, rest and education, as shown in the algorithm (Fig. 1), as well as optimism. This position paper is mainly focused on medical therapy, but other components of therapy need also be addressed. These non-pharmacological interventions should be considered a most significant part of the comprehensive management of RA patients [26].

The pharmacological options for the management of RA are summarized in Table 3.

Drug efficacy

Corticosteroids

Corticosteroids have proven effective in controlling the main signs and symptoms of RA, including joint pain and inflammation [72, 73]. Though not recommended as a single therapy for the treatment of RA, they can be very useful as bridge therapy to control symptoms of the disease, especially disease flares, and to improve patients' quality of life until the effects of specific DMARDs are achieved. Despite the results of recent trials on corticosteroid therapy for RA, most experts do not recommend the use of these agents as the sole disease-modifying agent [74].

The most commonly used agents are prednisone and prednisolone, administered mainly as a single morning dose. Deflazacort is a new-generation steroid available in several Latin American countries, which apparently causes fewer adverse effects with respect to bone metabolism. However, evidence of its efficacy in RA is not as robust as that of older agents. The dose equivalence proposed for deflazacort is 6 mg, for prednisone/prednisolone is 5 mg dose, and for methylprednisolone is 4 mg.

Low-dose steroids have been shown to delay the development of bone erosions [73, 75]. Low doses, ≤ 7.5 mg/day of prednisone or an equivalent, have shown good efficacy in the first 3 months. Prolonged use should be avoided. They can be used for short periods when disease flares occur. Low doses of prednisone can be used during pregnancy without risk to the fetus.

Patients on chronic corticosteroid therapy should receive supplementary hydrocortisone therapy before surgical procedures or during severe disease flares. The use of corticosteroids in Latin America poses particular risks associated with widespread self-medication practice and inefficient control of the sale of prescription medications, leading to inappropriate use of these agents. Accordingly, taking into account the clinical status of each patient, and under strict monitoring, physicians should use corticosteroids for the shortest period of time necessary.

Certain steroids (dexamethasone and betamethasone), as well as intramuscular deposit steroids, should be avoided. In the case of intramuscular deposit steroids, there is evidence that suggests potential benefit in some cases as initial bridging therapy [76]. Nevertheless, this practice should be restricted and strictly followed by rheumatologists in Latin America. It has been recognized by participants in the meeting that patients tend to use this intervention indiscriminately without any clinical supervision. Intra-articular deposit steroids are useful for the control of inflammation in one or two joints. High-dose corticosteroids (prednisone 1 mg/kg/day or equivalent agents) are used to treat severe extra-articular manifestations such as rheumatoid vasculitis. In some of these situations, cyclophosphamide is also needed.

Any patient starting low-dose steroid therapy should concomitantly receive supplemental calcium (at least 1500 mg/day) and vitamin D (400–800 U/day) [77]. The use of oral bisphosphonates has also been recommended for steroid-associated osteoporosis [77]. PANLAR participants have expressed concern about the frequent improper use and abuse of steroids, the consequences of which are well known to rheumatologists. Education is needed on how, when, and for how long to prescribe these agents.

Previous studies have demonstrated that the risk for infections increased up to eight times in patients who had received steroid therapy *vs* non-steroid-treated patients. Dosage apparently associated with a higher risk is >10 mg/day, or a cumulative dose of 700 mg. This information was confirmed by data obtained from patients with SLE [78] who had received steroids (≥ 40 mg/day), for whom the risk for infection increased up to five times that of patients not on steroid therapy. Since in most Latin American countries corticosteroids can be easily obtained, self-medication with these drugs poses a serious problem [79]. The influence of self-medication on the risk for infections and their severity must be taken into account.

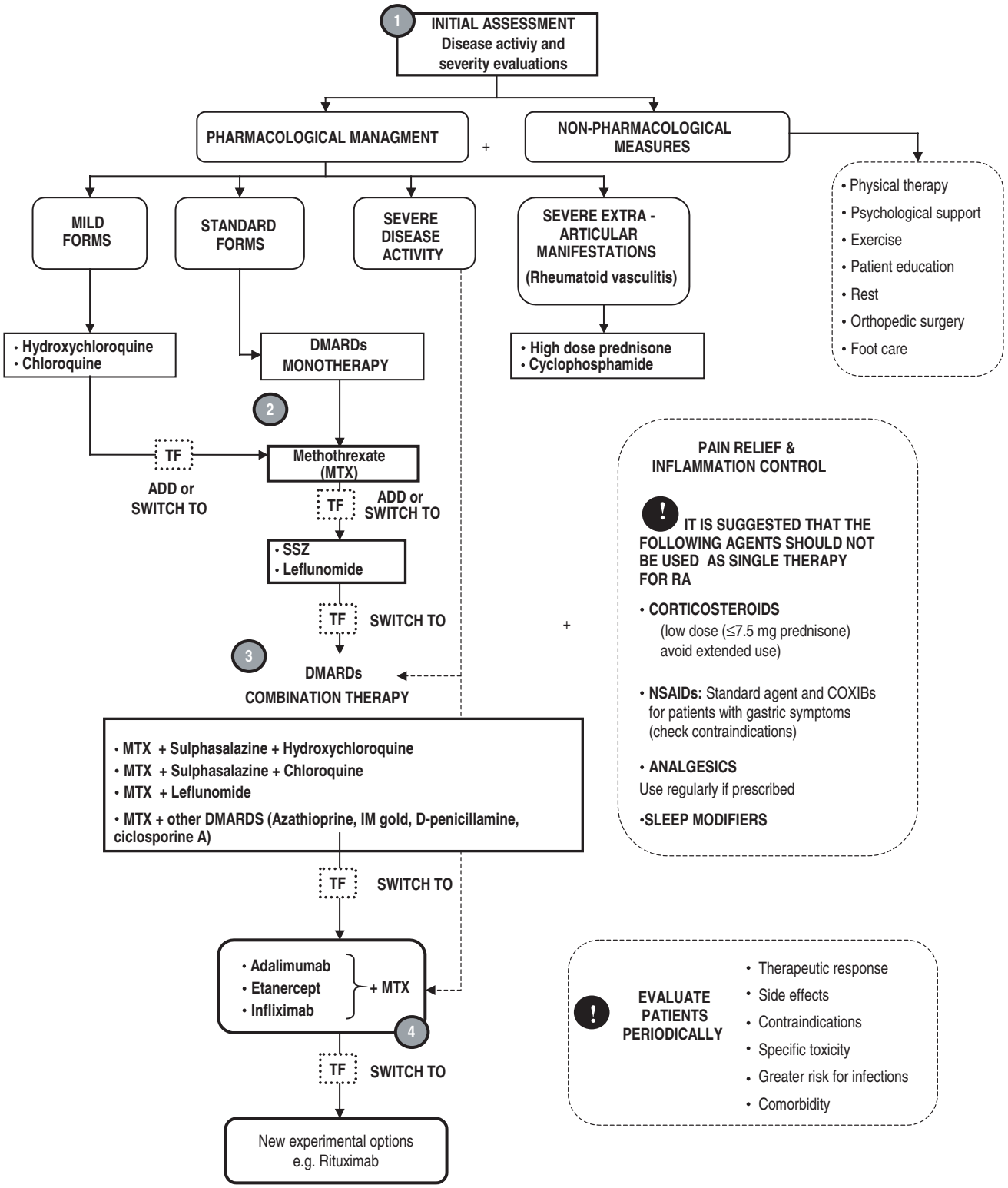

FIG. 1. Rheumatoid arthritis treatment. TF, treatment failure (with maximum-doses therapy after 8–12 weeks. Disease activity score 28: >3.2). Refer to the text for detailed information.

Non-steroidal anti-inflammatory drugs

These drugs are useful for pain relief and control of inflammation in RA patients. All of them have shown similar efficacy. They are not substitutes for specific arthritis drugs or DMARDs. There is no evidence that non-steroidal anti-inflammatory drugs (NSAIDs) modify the natural course of the disease, and NSAIDs combinations are not recommended. In addition, there is no evidence that topical NSAIDs are effective in RA. NSAIDs may be administered by intramuscular and rectal routes. Multiple agents in this class are available [80, 81]. Although it is almost impossible to issue a firm recommendation, some NSAIDs (including diclofenac, ibuprofen and naproxen) are considered to be more

Table 3. Pharmacological management of RA

	DMARDs	Biological agents	Steroids	NSAIDs*	Analgesics
Agents	Methrotexate (MTX), leflunomide (LEF), sulphasalazine (SSZ), antimalarials (chloroquine, hydrochloroquine), ciclosporin A, azathioprine, IM gold, D-penicillamine	Etanercept, infliximab, adalimumab, rituximab.	Prednisone, prednisolone, methylprednisolone, deflazacort.	Aspirin, ibuprofen diclofenac, naproxen, meloxicam, indomethacin, ketoprofen, COXIBs	Acetaminophen, narcotic agents.
Main effects/indications	Control disease activity, irrespective of disease duration. MTX drug of choice. LEF and SSZ options when MTX contraindicated or ineffective. Antimalarials for mild cases or in combinations. Cyclosporine A refractory RA.	Specifically directed against molecules involved in inflammatory process. Indicated for active RA after DMARDs failure, combined with DMARDs, or when DMARDs are contraindicated.	Control joint signs/symptoms, pain and inflammation, until DMARDs effect achieved. At low doses, delay bone erosion. At high doses, relieve severe extra-articular signs/ symptoms.	Control pain and inflammation. Do not modify RA natural history.	Only symptomatic pain relief. Preferably used on a regular basis, rather than as needed.
Adverse side effects	MTX: liver, bone marrow toxicity, pneumonitis, gastrointestinal (GI) effects, mucositis, alopecia, headache, increased infection risk. Antimalarials: ocular toxicity, GI effects, skin hyperpigmentation, rash, hair depigmentation, decreased appetite, rarely myopathy, neuropathy or heart block. SSZ: cytopaenias, GI effects, headache, liver toxicity, photosensitivity, rash. LEF: liver and bone marrow toxicity, GI effects including diarrhoea, mouth ulcers, alopecia, hypertension, weight loss. Ciclosporine A: renal toxicity, hypertension, gum hyperplasia, hypertrichosis. Azathioprine: bone marrow toxicity, liver damage, pancreatitis, hypersensitivity reactions. IM gold: bone marrow toxicity, nephrotic syndrome, skin reactions. D-penicillamine: Mucocutaneous reactions, haematologic toxicity, hematuria, nephrotic syndrome.	Rash, tachycardia, blood pressure changes. Rarely, anaphylactic reaction. Most serious effects: infections by intracellular microorganisms, bone marrow suppression, multiple sclerosis, tumours (lymphoma), heart failure aggravation. Increased risk of tuberculosis with anti-TNF.	Often improperly used or abused. Not recommended as single RA therapy. Dexamethasone, betamethasone and intramuscular deposit steroids should be avoided although some evidence suggests a potential use.	GI effects. NSAIDs combinations not recommended. Topical NSAIDs efficacy not demonstrated. Important to evaluate cardiovascular risk factors, particularly with COXIBs.	Narcotic analgesics can cause addiction. High-dose acetaminophen can cause liver damage. Some caffeine-containing agents taken near bedtime can interfere with sleep.

*NSAIDs mentioned here represent examples from different classes of agents.

beneficial in RA, and are supported by Type 1 and Grade A recommendations for their use in RA. Other agents include meloxicam, indomethacin and ketoprofen. Moreover, NSAIDs with intermediate half-life might be preferred for patients whose symptoms usually occur at night, during sleep.

NSAIDs can cause varied adverse effects, especially gastrointestinal effects. New specific cyclooxigenase-2 (COX-2) inhibitors (COXIBs) have proven as efficacious as other NSAIDs, sometimes with fewer gastrointestinal adverse effects [82]. Nevertheless, rofecoxib has been removed from the market because of cardiovascular toxicity. This special toxicity concern has also been raised for other COXIBs and also for some other NSAIDs. More studies will be needed to provide more conclusive recommendations. COXIBs should be prescribed mainly to patients with a history of gastric ulcers or haemorrhages, with age >65 yrs without cardiovascular and cerebrovascular risk factors, or with concomitant steroid therapy, warfarin use (strict monitoring) and evidence of *Helicobacter pylori* infection.

Analgesics

Analgesics are not useful for the control of RA activity; they are indicated only for symptomatic pain relief. They should not be used as substitutes for DMARDs. When prescribed, they need to be used regularly and not just when needed for acute pain episodes.

DMARDs

When should a traditional DMARD or a biological agent be prescribed?

Treatment with traditional DMARDs or biological agents should be instituted as soon as the disease has been diagnosed [83]. If diagnosis is delayed, these drugs should also be prescribed, since their therapeutic indication is based on disease activity rather than disease duration. Regardless, rheumatologists should initiate treatment with DMARDs or biological agents at an early stage of the disease, ideally within the first 2–4 months, since early therapy delays or minimizes functional deterioration and occupational disability [84].

Which DMARD should be used as a first option?

The choice of a drug for patients with RA should be made on a case-by-case basis. Disease activity, risk factors such as polyarthritis or RF+, psychosocial factors, and concomitant diseases should all be considered. The goal of RA treatment is remission. Unfortunately, this has not been achieved frequently with traditional DMARDs alone, but has been with TNF antagonists [85–88]. Physicians should be aware of this final objective and look for better outcomes in the long term.

At present, methotrexate (MTX) is considered the DMARD of choice for the majority of cases [83, 88–91]. Leflunomide (LEF) has proven effective in the control of disease activity [70] and can be considered, along with sulphasalazine (SSZ), as treatment options, especially when MTX is contraindicated or has provided inadequate responses [90, 92].

Hydroxychloroquine and chloroquine may be considered only for mild forms of the disease and for combination therapy with other DMARDs. However, treatment with these agents, as well as with minocycline, has not been shown to reduce progression of radiological joint damage [90].

Drugs associated with high toxicity, such as cyclophosphamide, and with low response rates, such as auranofin, should not be usually used for the treatment of RA [93, 94]. Cyclophosphamide could have an indication in severe rheumatoid vasculitis [91, 95].

Azathioprine has demonstrated efficacy in the treatment of RA, but its use has been limited by toxicity and risk–benefit considerations. In addition, in actual clinical practice, this agent, commonly in combination with MTX, is usually reserved for patients failing to respond to other DMARDs [90, 91]. D-penicillamine [96] and intramuscular gold [97, 98] are other DMARDs used by many rheumatologists in Latin America, although less frequently than other agents, as seen in other regions of the world [99, 100].

Ciclosporin A has been recommended for patients with refractory disease, when MTX has failed at maximal doses; however, its toxicity and the emergence of biological agents have limited its use considerably [90, 101, 102]. In case of therapeutic failure with one traditional DMARD, a second one should be used, and so on. A cautious trial period to consider drug failure is 8–12 weeks [90].

Combination therapy with two or three DMARDs should be considered for patients with severe disease activity at disease onset, or in the case of therapeutic failure with MTX at optimal maximal doses (20–25 mg/week) for at least 12 weeks or LEF has been documented [90, 103]. Observational information provided by several rheumatologists have acknowledged that these MTX maximal doses are not always well-tolerated by Latin American patients with RA. This intolerance should be investigated further. Subcutaneous and intramuscular routes are alternative ways of administration.

Biological agents

Biological therapies are the result of newer insights into the pathogenic mechanisms of RA and the application of biotechnology to the development of therapies specifically directed against molecules involved in the inflammatory processes of the disease. These agents represent the greatest advance in the control of RA in the last decade [104–115].

Biological agents currently approved for the treatment of RA include: etanercept, a soluble recombinant anti-TNF receptor construct, infliximab and adalimumab, both monoclonal antibodies against TNF, and anakinra, a receptor antagonist against interleukin-1 (IL-1) [116]. All three TNF antagonists—adalimumab, etanercept and infliximab—are available in most Latin American countries. Anakinra is not available in Latin American countries. Its effectiveness has not been as relevant as other biologics and even in countries where it is available, it is rarely used.

Rituximab and Abatacept may offer options for patients who no longer respond to TNF antagonists. It is likely that initially these two agents will be used in TNF failures [117].

Rituximab, a genetically engineered chimeric anti-CD20 monoclonal antibody, has been recently evaluated in a placebo-controlled, randomized, clinical trial in RA, with positive results, both as monotherapy and in combination therapy with MTX [118]. These results support the beneficial effect of B-cell depletion in RA therapy seen earlier, and a potential role for this agent in RA [119]. It should be noted that recent data indicate that repeated use of rituximab in a 4–5 yr period is associated with significant reductions in immunoglobulin concentrations [120]. This could be associated with the increased risk of chest infection that has been suggested to exist in RA patients treated with this agent. Such respiratory episodes may be not caused by infection, but may be some form of delayed sensitivity reaction.

Abatacept is a selective costimulation modulator that has shown efficacy in preclinical studies in animal models of autoimmune disease, and has recently been assessed in the treatment of RA, which has remained active despite MTX therapy [121]. Abatacept therapy combined with MTX was associated with sustained clinical benefits for 1 yr, without major safety issues. Nevertheless, this agent is not currently available in Latin America.

The decision to start treatment with a biological agent should be considered on a case-by-case basis after assessing factors such as disease activity, therapeutic failure with DMARDs, economic variables that could jeopardize long-term treatment, and patients' preferences. The rheumatologist should provide the patient with all the relevant information about risks and consequences of inadequate therapy.

The rheumatologist must also acknowledge the patient's right to participate in the choice of treatment, since in certain cases, economic or social factors might influence the rheumatologist's recommendations.

Although there is evidence that anti-TNF agents in combination with MTX are superior in efficacy to MTX alone, because of the lack of information on long-term efficacy and toxicity beyond 8 yrs, and especially because of higher relative costs, particularly in Latin American countries, these agents cannot be recommended as first-choice drugs for the treatment of RA.

Indications for TNF antagonists are:

(1) Treatment of active RA, after a proven therapeutic failure with a DMARD, such as MTX, given at maximal doses for an acceptable period of time (8–12 weeks).
(2) As first-line therapy when traditional DMARDs are contraindicated. (Nevertheless, it is better to prescribe biological agents with MTX *vs* as monotherapy.)

Contraindications for the use of biological agents include pregnancy and breastfeeding; active infection; patients at high risk of infection (chronic leg ulcers, previous tuberculosis, septic arthritis in the last 12 months, sepsis of a prosthetic joint, persistent or recurrent chest infections, indwelling urinary catheter, multiple sclerosis); and malignancy (with the exception of basal cell carcinoma or malignancies diagnosed and treated more than 10 yrs before) [122].

There is no specific recommendation on which TNF antagonist to use, since none of these agents has proven superior to the others in terms of efficacy or safety. It has also been shown that non-responders on one TNF antagonist may benefit from switching to another TNF antagonist [123–125].Current therapies are unsatisfactory in most patients, since they do not modify the course of the disease. In most cases, they simply delay disease progression, and responses are not sustained long term. Although biologics are already available in clinical practice, some important questions on their use need to be answered, including:

(1) How long should biological therapy be used in patients with positive therapeutic response?
(2) If response is suboptimal, should dosage be increased or dosage periods reduced?
(3) If biological agents delay joint damage significantly, should these agents be prescribed as first-choice therapy on the grounds of this effect? [126–128].
(4) Can biological agents be used as induction therapy, and be replaced afterwards with conventional DMARDs?
(5) Can doses lower than those currently recommended be used?
(6) Can intervals between doses be extended?
(7) Should risk factors be considered to stratify patients into clinical subgroups with various indications for biological agents?
(8) Can concomitant doses of MTX and corticosteroids be reduced in case of good clinical response to TNF antagonists?

The answers to some of these questions, as well as to others that will surely come up, are likely to arise from future studies and from some already in progress. In addition, the implementation of the recommendations made by this position paper should include careful monitoring of the efficacy and safety of the different therapeutic options proposed. This will help to elucidate some of the questions regarding the use of biological agents in the treatment of RA.

Combination therapy

Rheumatologists have gained experience with several combinations of DMARDs. This strategy has some theoretical and practical implications [103]. Most combinations include MTX as the anchor medication. Many of them have been evaluated and some of them deserve special mention. A scheme proposed by O'Dell *et al*. [129] with MTX, SSZ and hydroxychloroquine has been published with encouraging results. It has been discussed that this combination using chloroquine instead of hydroxychloroquine could be tried in patients before treatment with a biological agent is initiated.

Another combination with significant results includes MTX plus LEF. It is highly effective, although special caution is needed to monitor liver and bone marrow toxicity [130].

Recent trials have shown that TNF antagonists with MTX could be the most common combination in developed countries in the near future. If these agents fail to obtain the desired therapeutic effect, they can be changed to another TNF antagonist, and good efficacy can be achieved [85, 131]. If this also fails, other therapeutic options can be tried. New promising agents are under study.

Drug toxicity and monitoring

All medications used for RA can cause adverse events. Patients should be adequately informed about this. Therapy should be closely monitored, and physicians should seek an appropriate risk/benefit balance on an individual basis. Effects of DMARDs on fertility, pregnancy and breast-feeding are summarized in Table 4.

Antimalarials

These drugs have the best safety profile [132, 133] and are widely used in Latin America, particularly chloroquine because of its low cost. The most feared adverse event is ocular toxicity, such as blurred vision, maculopathy and corneal deposits. The most frequent adverse events are gastrointestinal (e.g. nausea, abdominal pain and diarrhoea) [132]. Skin hyperpigmentation, rash, hair depigmentation, loss of appetite and, rarely, myopathy, neuropathy and heart block may also occur [26, 132, 133].

Baseline ophthalmologic evaluation is recommended [132, 133], particularly in patients older than 60 yrs of age. To decrease the risk of ocular toxicity, chloroquine and hydroxychloroquine should not be given at doses above 4 mg/kg/day and 6 mg/kg/day, respectively. Ocular toxicity should be screened for annually through ophthalmologic evaluations, including assessment of visual field [134].

Methotrexate

MTX is considered the gold standard of RA therapy because of its adequate profile of efficacy and safety when properly used [26, 132]. Adverse events are hepatotoxicity, bone marrow toxicity and pneumonitis. Other frequent adverse events are nausea, mucositis, diarrhoea, alopaecia, headache and infections [26, 135].

Baseline evaluation. It should include a complete blood cell count (CBC), serum creatinine, liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST)] and chest X-rays. Patients at risk should also have serology for B and C hepatitis [26, 134].

Table 4. Effects of DMARDs on fertility, pregnancy and breast-feeding

Drug	Fertility	Pregnancy	Breast-feeding	Advise
Azathioprine	No effect	Contraindicated	Contraindicated	Contraception
Cyclophosphamide	Ovarian failure	Contraindicated	Contraindicated	Contraception
Ciclosporin A	No effect	Contraindicated	Contraindicated	Contraception
Hydroxychloroquine Chloroquine	Undetermined	Caution	Caution	Can be used with caution
Corticosteroids	No effects	Minimal doses	Minimal doses	Calcium + Vitamin D supplementation
LEF	Undetermined	Contraindicated	Contraindicated	Contraception
MTX	No effect (female) Reversible Infertility (male)	Contraindicated	Contraindicated	Folic acid supplementation. Stop 3 months before pregnancy is planned
Mynocicline	Undetermined	Contraindicated	Contraindicated	As other tetracyclines
D-penicillamine	Undetermined	Contraindicated	Contraindicated	Few data
IM gold	No effect	Caution	Caution	Do not start if pregnancy is desired
SSZ	Same as MTX	Possibly no effect	Caution	

Monitoring. CBC count and liver function tests every 4–8 weeks and serum creatinine every 6 months is recommended [26, 135].

Additional recommendations. Risk factors for liver disease are treatment duration, obesity, alcohol abuse, history of B and C hepatitis and the concomitant use of hepatotoxic medications. When liver enzymes are increased less than twice the upper normal value, it is recommended to repeat these tests in 2–4 weeks. If liver enzymes are increased 2–3 times the upper normal value, it is recommended to decrease the dose and repeat measurements every 4 weeks. If ALT and AST concentrations are persistently high after two measurements, it is recommended to stop MTX [26]. Folic acid should be given to all patients at a dose of 1 mg/day [136]. Patients should be advised to seek medical care in case they develop dry cough and fever, since this clinical finding could be a result of MTX-induced lung injury (pneumonitis), a potentially fatal adverse effect of MTX [137].

Sulphasalazine

SSZ has an acceptable safety profile. The most serious adverse events are cytopaenias [26, 132, 135]. The most frequent adverse events are nausea, upper abdominal complaints, headache, liver toxicity, diarrhoea, photosensitivity and rash [26, 132, 134, 135].

Baseline evaluation. CBC count, serum creatinine, liver function tests [135, 136].

Monitoring. CBC count and liver function tests every 4–8 weeks (twice) and then every 3 months [26, 134].

Leflunomide

The most serious adverse events are liver and bone marrow toxicity. Other adverse events include nausea, diarrhoea, mouth ulcers, alopaecia, high blood pressure and weight loss [26, 134, 138].

Baseline evaluation. CBC and liver function tests. Patients at risk should also have B and C hepatitis serology [26, 134].

Monitoring. CBC and liver function tests every 4 weeks for the first 6 months and then every 8 weeks thereafter. Serum creatinine concentration should be measured every 6 months [26, 134].

Additional recommendations. If ALT and AST concentrations increase less than twice the upper level, testing should be repeated in 2–4 weeks. If liver enzymes increase 2–3 times the upper level, the dose should be reduced and the test repeated every 4 weeks. If ALT and AST continue to be 2–3 times above the upper normal level, in two subsequent measurements, LEF should be stopped. In case of severe liver toxicity and bone marrow toxicity, cholestiramine 8 g tid for 11 days can be useful. It is recommended that plasma concentrations be lower than 0.02 mg/l.

Other DMARDs

Other DMARDs, such as azathioprine, parenteral gold, D-penicillamine, ciclosporin A and cyclophosphamide, are less frequently used because of toxicities, including hepatic damage, pancreatitis, hypersensitivity reactions, cutaneous rash, stomatitis, bone marrow suppression, hypertension, renal insufficiency, hirsutism, hypertrichosis, gingival hyperplasia, lymphoproliferative disease, leucopaenia and thrombocytopaenia [90].

Mynociclin is not commonly used in Latin America, thus the discussion of its toxic effects exceeds the scope of this publication.

Biological therapy

The most serious adverse events are infections by intracellular microorganisms, mainly tuberculosis (TB). Other reported adverse events are bone marrow suppression, multiple sclerosis, tumour development (particularly lymphomas), and aggravation of heart failure [26, 136, 139]. The most frequent adverse events are local reactions in subcutaneous use and during infusions, such as rash, tachycardia and blood pressure changes. Anaphylactic reactions have been reported rarely. Because of these rare reactions, biological agents should be given under strict surveillance, and rheumatologists should provide immediate care if needed [26].

Baseline evaluation. Careful evaluation for latent TB through a detailed medical history, chest X-rays, and purified protein derivative (PPD) skin testing [140, 141].

Additional recommendations. Before treatment with biological agents is started, active acute and chronic infections should be excluded.

Agents that block TNF action and recombinant IL-1 represent an important advance in the treatment of RA and other inflammatory diseases of immune origin. These agents are specific to their cytokine targets, but inhibiting these specific targets may have other negative consequences associated with a disruption of the immune system. These agents have been associated with

a higher risk for opportunistic and non-opportunistic infections [107], despite similar overall rates of serious infections in the RA populations treated and not treated with biologics [142, 143]. With Latin America's heterogeneous ethnicity, lower socio-cultural and educational levels, and limited access to healthcare, prospective trials are needed to evaluate the impact of different factors associated with a higher risk of infections to establish the magnitude of their individual or combined effects. On the other hand, it is essential to evaluate other predisposing factors, such as comorbidity with chronic diseases.

It is also essential to know the regional distribution of certain endemic diseases (mycobacterial infections, listeriosis, hystoplasmosis, cryptococcosis, etc.), and to individualize regional risks accordingly.

Tuberculosis (TB) and anti-TNF treatment

TNF plays an essential role in the formation of the tuberculous granuloma, which is associated with the prevention of dissemination of the disease. Reduction in the activity of TNF can lead to impairment of this mechanism, with the subsequent reactivation of latent TB.

Patients considered at high risk include:

(1) Patients with a diagnosis of TB who have not completed optimal anti-TB treatment
(2) Tuberculin skin test >5 mm or vesicle (without BCG vaccine and without a history of active TB in the last 10 yrs in both cases)
(3) Abnormal chest X rays
(4) Positive tuberculin test (10 mm or more) with previously negative tests
(5) Decisions regarding the following points should be made jointly with infectious disease services in each country:

- Duration of chemoprophylaxis in patients with risk factors for TB, with or without latent infection.
- Patients on biological therapy who develop TB. By the end of anti-TB therapy, these patients should be evaluated to assess the possibility of resuming biological therapy.
- Pertinence of vaccination before beginning biological therapy.
- A negative PPD does not preclude latent TB infection in patients with RA. Recent information from Peru supports this notion [144].

Recommendations for the detection of latent TB have been published by the Infectious Disease Society of America [145]. Other opportunistic infections associated with biological therapy include listeriosis, hystoplasmosis, *Pneumocystis carinii* infection, aspergillosis, cryptococcosis, candidiasis and coccidioidomycosis.

Infections in RA patients treated with biological agents may present as a subclinical disease or as an atypical clinical entity. Therefore, it is important to:

(1) maintain adequate clinical observation,
(2) educate physicians on the treatment of these patients,
(3) educate patients,
(4) document the suspected infection (cultures) and begin treatment as soon as possible,
(5) consult other specialties as required,
(6) use biological agents as treatment when indicated with monitoring by qualified rheumatologists,
(7) ensure that the patient has regular clinical and laboratory assessments from a qualified rheumatologist; and
(8) consider isoniazid prophylaxis for patients who receive prednisone dosing >10 mg/day.

In Latin America, it is appropriate to develop an RA surveillance and database system, including therapy with biological agents. This will contribute to:

(1) develop a program for post-commercialization and epidemiologic surveillance and
(2) develop a prospective epidemiologic study that will clarify unanswered questions in Latin America.

Since information on these issues is lacking, studies on a multinational cohort with demographic representation, such as the one initiated by the Latin American Rheumatoid Arthritis Group (Grupo Latino Americano De Artritis Reumatoide, GLADAR), will help answer many of the current questions.

Non-pharmacological interventions

Non-pharmacological interventions are most important in the comprehensive management of RA patients, but are beyond the scope of this paper. The reader should look at the references mentioned subsequently for more detailed information.

Team care for patients with RA has been shown to be both necessary and effective. This includes non-pharmacological interventions at a same level of importance as medication in achieving the final goal of improving health-related quality of life in these patients [146].

Physical therapy and exercise have been shown beneficial for RA patients. In a study by Hakkinen *et al*. [147] muscle strength increased with strength exercise during a 2-yr training period. This favourable effect persisted during a subsequent period of self-monitored exercise at home. Another study showed that a long-term, high-intensity exercise programme was more effective in improving RA patients' functional ability when compared with standard physical therapy [148]. This programme was not associated with a worsening of radiographic damage of the large joints. Rheumatologists, physical therapists and patients have acknowledged the effectiveness and safety of moderate and high-intensity exercise for RA patients [149].

Occupational therapy has also been evaluated in RA management with various results, although the traditional physical therapy/occupational therapy model has been shown to have some benefits in patient outcomes when delivered by rheumatology-trained therapists [150].

Therapeutic use of ultrasound has not proven effective in RA patients [151]. Overall, data on the effectiveness of rehabilitation interventions in RA are scarce, and more well-designed research is needed to make firm recommendations [152].

Non-pharmacological interventions should also include careful management of foot and ankle involvement, as well as early appropriate therapeutic interventions, which should help maintain active ambulatory functioning [153].

Surgery has also a role in the management of patients with RA, using various orthopaedic surgery procedures, including total joint replacement, as has been described by Massardo *et al*. [154].

Conclusions

RA is a major, yet under-recognized health problem in Latin America and the Caribbean.

Epidemiological and clinical characteristics of RA vary in different regions, probably because of mixed ethnicity and genetic background.

Various economical and educational factors hinder the appropriate management with timely diagnosis and therapy of RA.

DMARDs are the currently recommended agents for the treatment of RA patients.

Recently developed biological agents have proven to be excellent therapeutic options, although additional evidence is needed on their use in the region, as well as on epidemiology, risk factors, comorbidity, quality of life, infections risk, use of resources, mortality, and pharmaco-economics. Also, recognition within professional and healthcare organizations is needed. Importantly, the Pan-American Health Organization's (PAHO) publication 'Health in the Americas' (2002 edition) does not mention RA as a major health problem in the region [5].

A common agenda for the implementation of RA community education programmes should be developed, along with the promotion of an International RA Day and Month with efficient publicity and information dissemination via mass media. Such initiatives should be submitted to international agencies including PAHO and the Economic Commission for Latin America (Comisión Económica para América Latina, CEPAL). National Associations of Rheumatology, as well as diverse government and private organizations and agencies, should also be included in these initiatives. Medical education programmes should be developed in collaboration with medical schools and included in pre- and post-graduate curricula.

It is important to educate the community, physicians, medical students and health personnel on the characteristics and initial clinical features of RA and on the importance of early therapy. An effective cycle would involve (1) raising awareness among patients adequately through mass media campaigns, (2) patients consulting with the most readily available physicians within 2 months of the onset of the initial symptoms of RA, (3) these physicians establishing correct diagnoses and referring patients to rheumatologists rapidly and (4) rheumatologists prescribing specific therapy with DMARDs that can be initiated within the first few months of the onset of symptoms.

Some possible solutions to improve therapy access are decreasing custom fees and taxes for drugs, prostheses and orthoses. In addition, the development of quality generics or the use of manufacturers' drugs with lower or preferential prices according to the region could also enhance appropriate management of RA. Stratified cost evaluations of therapy could be instrumental in promoting such efforts. Also, strong evidence of the clinical and economic benefits of early RA therapy should be collected to prompt decision makers in the region to adhere to and support these initiatives.

A relevant questionnaire will be sent to each Latin American Rheumatology Society through its representatives participating in the meeting. This document has been endorsed by all Latin-American Associations of Rheumatology and PANLAR.

Rheumatology	Key messages
	• In Latin America and the Caribbean, the impact of RA on individuals' quality of life and healthcare costs is under-recognized by health authorities and physicians. • Early, aggressive therapy improves long-term outcomes in RA patients.

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This document summarizes the final report of the First Latin American Consensus for the Treatment of RA developed in Quito, Ecuador, in 12–14 September 2003. All Latin American Rheumatology Associations registered in PANLAR were invited to participate, and attending PANLAR members were divided into six groups. Coordinators identified essential topics and supporting literature to be reviewed, analysed pertinent data, and finally discussed and agreed upon courses of action in plenary sessions.

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