A Survey of Barriers to Treatment Access in Rheumatoid Arthritis

in

Major Latin American Countries – Argentina, Brazil and Mexico

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Executive summary

The objective of this report was to identify potential barriers to treatment access for patients with rheumatoid arthritis (RA) in Latin America through the examples of Argentina, Brazil and Mexico. This study follows the methodology used in a previously conducted European report labelled *A Survey of Barriers to Treatment Access in Rheumatoid Arthritis[i].* To assess the barriers to treatment access, structured desk research was consolidated by semi-structured, qualitative telephone interviews with senior treating physicians and patient representatives to examine how closely each phase of the treatment pathway – diagnosis, treatment and monitoring – followed best-practice recommendations by the European League against Rheumatism (EULAR).

To assess the barriers to treatment access, health care and reimbursement systems as well as diagnosis and treatment patterns will be analyzed. The results from this study may serve as a help to governments and medical societies in identifying areas in need of improvement in order to increase treatment access for patients with RA in Latin America.

The burden of rheumatoid arthritis: RA is a chronic disease with a high burden of pain, fatigue, reduced function and lowered quality of life. At the societal level it also comes with a productivity burden. Studies indicate that one third to one half of those affected is forced to quit the workplace within ten years of onset. Data from Latin America suggest that disease onset occurs on average at the age of 40 and the estimated prevalence in the region is approximately 0.2%-0.5%.

Goals of treatment: In addition to symptomatic alleviation with corticosteroids and non-steroidal anti-inflammatories, disease-modifying anti-rheumatism drugs (DMARDs) have revolutionized therapy from their first introduction in the 1980s by allowing the disease process itself to be targeted. These agents comprise both "conventional" small molecule DMARDs and biologic agents that were first introduced in the 1990s. The availability today of multiple drugs and drug classes has rendered disease remission to be the goal of treatment, as explicitly defined by EULAR and accepted internationally.

Disease diagnosis: Both desk research and interviews established that delays in RA diagnosis are one of the most significant barriers to initial treatment access. EULAR recommends that those patients presenting RA should be seen by a rheumatology specialist within 6 weeks of symptomatic onset, and none of the countries investigated met this criterion. Delays are attributable to shortages in available rheumatologists specifically in rural areas; and the structure of health care system. The methodology of

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[i] www.comparatorreports.se

diagnosis was similar between the countries but not at all times compliant with EULAR recommendations, especially when it comes to anti-CCP testing and imaging.

Treatment: All countries follow the EULAR recommendation to initiate DMARD treatment with methotrexate, and all reserve biologics for second or – more commonly – later lines of treatment after insufficient response to one or more DMARDs. Before biologics, it was also common to receive anti-malarias and corticosteroids. Treatments are most often changed for lack of response. In each country the first biologic used is almost always an anti-TNF, based on the length of clinical experience with this class and the fact that it is the most reimbursed class in the region. For second or third biologic, the anti-TNFs were rotated or abatacept or rituximab were given. Significant restrictions exist on access to biologic agents in most of the countries studied, relating to budgetary caps and funding restrictions at the national and/or local levels, and availability of authorised prescribing centres.

Treatment monitoring: Treatment monitoring varied considerably in its alignment with EULAR recommendations. Some evidence suggested adherence in Argentina and Mexico but not in Brazil, mainly due to the limited access to specialist treatment in rural areas and longer waiting times within the public health care system.

Conclusions: In all three countries investigated, significant barriers to RA treatment were identified relating to general access to care, access to specialists (and thereby diagnosis) and access to biological treatment.

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1.   Glossary and Abbreviations

Abatacept (Orencia®) Manufactured and marketed by Bristol–Myers Squibb. Orencia is a T-cell co-stimulation modulator, which inhibits T-cell activation by blocking interactions with CD28. It is administered by intravenous infusion.

ACR   American College of Rheumatology http://www.rheumatology.org/

Adalimumab (Humira®) Manufactured and marketed by Abbott. Humira is an anti-TNF administered via subcutaneous injection twice a month.

AFIP   Federal Administration of Public Revenues in Argentina

AMIS   Asociación Mexicana de Instituciones de Seguros – Mexican Association of Insurance Institutions

ANMAT   Drug, Food and Technology National Administration – regulatory agency responsible for drug marketing and authorization in Argentina

Anti-CCP/ACCP Anti-cyclic citrullinated peptide, antibodies that can suggest a diagnosis of RA.

Anti-TNFs   Biologic anti-rheumatic drugs which target tumour necrosis factor (TNF, see below).

APAC   Authorization for High Complexity Procedures is a unit which represents one month treatment for one patient in Brazil

APE   Administración de Programas Especiales (Argentina) - Special Programs Administration

Biologics   In this monograph, 'biologics' refers to a group of DMARDs that are derived from biologic molecules such as antibodies or receptors. They modulate the disease process by directly targeting signalling pathways, cytokines, receptors and other mediators contributing to the pathogenesis of RA. Current biologics include anti-TNFs (adalimumab, etanercept, infliximab, golimumab, certolizumab), B-cell targeted therapies (rituximab), a T-lymphocyte co-stimulation modulator (abatacept), an anti-IL6R (tocilizumab) and an IL-1 inhibitor (anakinra).

CBM   Catálogo Básico de Medicamentos (Mexican Basic Drug Formulary)

CNPSS   Comisión Nacional de Protección Social en Salud (Mexico)– National Commission on Social Health Protection

CRP   C-reactive protein. A serum marker of systemic inflammation.

COPCORD   Community Oriented Programme for Control of Rheumatic Diseases (Brazil)

DAS   Disease activity score. The following parameters are included in the calculation: number of tender joints, number of swollen joints, erythrocyte sedimentation rate (ESR) and patient assessment of disease activity. The

	DAS provides a number between 0 and 10, indicating how active the rheumatoid arthritis is at any given time
DAS28	A version of the DAS based on a 28 joints which is commonly used to measure disease activity in RA. A DAS28 of <2.6 is typically used to define clinical disease remission, though other clinical definitions exist.
DMARD	Disease-modifying anti-rheumatic drug. Any of a class of therapeutic agents of widely variable structures and mechanisms of action that act on one or more of the underlying causes of RA to slow disease progression. There are two basic categories of DMARD: synthetic or traditional agents, and biologic agents. DMARDs are distinct from symptomatic RA treatments such as NSAIDs or COX2 inhibitors, which treat pain and inflammation without altering disease progression. In this monograph, the term DMARD refers to traditional small-molecule agents; biologic DMARDs are referred to as biologics.
Etanercept (Enbrel®)	Manufactured by Amgen. Marketed by Amgen/Wyeth. Enbrel is an anti-TNF administered subcutaneously, once or twice weekly.
ESR	Erythrocyte sedimentation rate. The rate, in mm/hour, at which red blood cells precipitate in uncoagulated blood. The ESR is a common haematological test used as a non-specific measure of inflammation.
EULAR	European League Against Rheumatism. http://www.eular.org/
FSR	Redistribution fund within the AFIP in Argentina with the purpose of transferring money from wealthier to poorer OS
GDP	Gross Domestic Product
GP	General practitioner.
HAQ	Health assessment questionnaire.
HMO	Health maintenance organization
HTA	Health Technology Assessment
IMSS	Instituto Mexicano del Seguro Social (Mexican Social Security Institute)
INEGI	Instituto Nacional de Geografía y Estadística (Mexico) – National Institute of Geography and Statistics
Infliximab (Remicade®)	Manufactured and co-marketed by Centocor and Schering-Plough. Remicade is an anti-TNF administered by intravenous infusion.
ISSSTE	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (Mexico) - Institute for Social Security and Services for State Workers
Joint erosion	Localised loss of bone substance within a joint, due to joint-related osteoporosis or growth of inflammation-associated fibrous tissue.
MH	Ministry of Health

MRI	Magnetic resonance imaging.
MTX	Methotrexate. A synthetic DMARD that acts as an inhibitor of folic acid and of purine metabolism.
NSAID	Non-steroidal anti-inflammatory drug.
OECD	Organization for Economic Cooperation and Development
OS	Obras Sociales – the social health insurance sector in Argentina
PAMI	Nation wide social health insurance fund for retired workers in Argentina
PEMEX	Health Service Institute of Petróleos Mexicanos
PMO	Compulsory Medical Plan (Spanish acronym) in Argentina, which is the minimum package guaranteed to all formal workers.
PPP	Purchasing Power Parity
RA	Rheumatoid arthritis.
RF	Rheumatoid factor. An autoantibody directed against immunoglobulin G. About 80% of patients with RA are seropositive for RF, and its presence predicts a more aggressive, destructive course.
Rituximab (MabThera®)	Manufactured by Genentech and Biogen Idec. Marketed by Genentech and Roche. MabThera, called Rituxan® in the US, is a B-cell modulator administered by intravenous infusion.
SAR	Argentinean Society of Rheumatology
SBR	Sociedade Brasileira de Reumatologia www.reumatologia.com.br/ - Brazilian Society of Rheumatology
SCTIE	Secretariat for Science, Technology and Strategic Inputs (Brazil)
SINAIS	Sistema Nacional de Información en Salud (Mexico) – National Health Information
SPSS	System for Social Protection in Health (Mexico)
SSS	Superitendence of Health Services, a part of the Argentinean MH
SUS	Sistema Único de Saude (Unified Health System - Brazil)
Swollen joint	A joint that is swollen on physical examination.
Tender joint	An inflamed joint that is painful when pressed.
TNF	Tumour necrosis factor. A cytokine involved in the inflammatory reaction of the immune system.
WHO	World Health Organization

2.   Introduction and rationale

Rheumatoid arthritis (RA) (ICD-10 M05, M06) is a chronic inflammatory joint disease that can affect virtually all joints, but most commonly involves the hands and feet. Other frequently affected joints include the wrist, knee and other large joints of the extremities. Onset can be gradual or acute, but in the majority of patients the course is progressive, leading to destruction of joints, functional disability and reduced quality of life. RA is also associated with a range of extra-articular manifestations, and patients with RA have increased morbidity and mortality compared with the general population, mostly due to the cardiovascular consequences of chronic inflammation and an increased frequency of lymphomas in relation to the severity of the disease [1]. It has been acknowledged that RA can have a significant impact on health related quality of life, mortality and is associated with increased healthcare costs when compared to normal population [2].

RA predominantly affects women (70–80% of cases) and disease onset is most common between the ages of 40 and 50 years, although RA can affect younger populations including children and adolescents [3]. Studies have indicated that the average age at disease onset is somewhat lower in Latin America compared to Europe [4]. Patients often cope for many years with the effects of the disease, in terms of restricted function, chronic pain and fatigue, and many (35–50%) are unable to work within 10 years of disease onset [5-7].

The prevalence of RA is generally estimated at 0.5–1.0% of the adult population in Europe [8], but ranges from 0.2% to 3.0% in published studies, with differences reported between and within countries. Studies of the prevalence of RA in Latin America report a higher prevalence of the population of European ancestry than African and Asian [4]. Overall, the reported prevalence lies between 0.2%-0.5% for patients older than 15 years in Latin America [4, 9-12].

Treatment of RA is both symptomatic (corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs]) and targeted at the disease process (disease-modifying anti-rheumatic drugs [DMARDs]) [13]. Conventional (non-biologic) small-molecule DMARDs (hereafter referred to as DMARDs) have been available since the 1980s. One of these, methotrexate (MTX), became the mainstay of RA treatment in the 1990s, with increasing use earlier within the disease course. The late 1990s saw a revolution in the management of RA with the introduction of biological DMARDs (hereafter referred to as biologics). A vast body of research with these drugs has shown that early treatment, in particular for active and erosive disease is crucial. Joint erosions start within the first months of symptoms, and early intervention with potent drugs has the ability to induce remission or considerably slow the disease process. It has hence become increasingly important to identify those patients with a poor prognosis early in the course of their disease to be able to maximize the effect of biological treatments.

There are currently three biologics that are widely used in Latin America (etanercept/Enbrel®, infliximab/Remicade® and adalimumab/Humira®). Additionally,

rituximab/MabThera® and abatacept/Orencia® are also licensed and used, mostly as second or third biological treatment.

A range of factors may contribute to the accessibility to these biologic treatments in the Latin American countries. As these drugs are marketed into a global market, with a similar price across the world, the difference in access may be driven by the national wealth of different countries (GDP). According to World Bank data, the average GDP per capita is 8,415 US$ (PPP term 2005) in South America with an average health care spending of 7% of GDP, with a wide range between countries. This can be compared to a GDP per capita of 26,404 US$ and a health care spending of 10% of GDP in OECD-Eurostat countries. In Latin America, the complexity and financing of health care systems is an important determining factor to access of services and medications. Details of the organization of health care systems of the countries under study are discussed later in the report. In short, the factors influencing access includes:

♦   Health care and reimbursement system – including GDP and health care expenditure across regions, time to pricing and funding decisions, treatment guidelines and economic analyses and HTA appraisals [14]

♦   budget constraints

♦   restrictions of prescription eligibility

♦   inadequate disease awareness in the general public

Regulatory and market access processes (pricing, funding, use) are aimed to provide a transparent and efficient framework to deliver innovation to patients and to make best use of societal resources. Treatment guidelines are often created for this purpose, for example at the European level, recommendations are developed and published by the European League Against Rheumatism (EULAR) [15]. The EULAR recommendations, which encompass diagnostic work-up, treatment initiation and patient follow-up, are formulated by an experienced panel and can be considered a benchmark among RA treatment guidelines, with strong peer influence. Although these are European, they have strong influence across the world on national guidelines. Still, the application of national and EULAR guidelines may be influenced by the level of available resources such as the number of specialists or imaging hardware that may influence diagnosis and early treatment and may vary across countries and regions. Similarly, the point of access to care (for example, general practitioners – GPs – as gate keepers) and referral systems will influence the time to diagnosis and bureaucratic application processes may delay initiation of biologic treatment where adequate. Even the time to treatment with classical DMARDs may be too long. Drugs in RA may hence not be prescribed and used even if they are approved, funded and recommended by national guidelines [16-18].

These issues make it relevant to investigate the barriers for access to care in Latin America in order to inform of which factors to address in order to improve access to RA treatment. This report describes some of the barriers to RA treatment access in three Latin American countries (Argentina, Brazil and Mexico) and summarizes levels of

adherence to the EULAR guidelines from 2007. It should be noted, however, that the EULAR guidelines are currently being updated to include newer biologics, such as tocilizumab, but these changes are not expected to affect the recommendations used for comparison in this report.

3. Objectives

In order to expand on a previous report on barriers to RA treatment access in Europe, the objective of the current study was to describe the organization of care, identify organizational and financial hurdles to access to care; and explicit and implicit limitations in access in three Latin American markets – Argentina, Brazil and Mexico.

4. Methods

For each country included in the study, desk research on RA and its treatment was followed by qualitative interviews.

- ♦ Desk research included publicly available sources on:
    - o Epidemiology
    - o Health Care Resources (health care professionals, facilities)
    - o Health Care System Information (Delivery of care, market access, funding)
    - o Guidelines
- ♦ The interviews were semi-structured one-on-one interviews of specialists (hospital- and office based) and GPs. Patient representatives were included in some cases.

Potential respondents were identified by local Research Consultancy companies on behalf of i3 Innovus (IECS in Argentina, MedInsight in Brazil and GuiaMark in Mexico). The local researchers (fluent in the local language) took responsibility for identifying respondents and conducting interviews in their respective country. Some respondents were sourced through recommendations by other respondents or own contacts. The main criterion for selecting local decision-makers was their apparent experience in treating patients and being aware of or involved in health policy efforts to improve RA care in the respective country. A further consideration was the achievement of broad geographical representation across each country.

Potential respondents were contacted by the local researcher by telephone or email and invited to participate. A standard letter confirming the invitation was sent to each potential respondent, and those responding positively were subsequently contacted by the local researcher.

Although a common interview guide was used, the semi-structured approach was intended to allow interviewees to expand on areas of particular interest or expertise. Not all interviewees were able to provide comprehensive responses on every topic, due to their specialties. Collectively, however, the interviews provided adequate coverage of all topics. In the few instances where significant information gaps were apparent after gathering all responses, i3 Innovus has researched and included supplementary narrative, with the aim of providing reasonably comprehensive and balanced coverage of all topic areas across the three countries.

The main report describes the collective findings from this study with comparison across the investigated countries. The country annex reports (one for each country) presents the country specific findings and hence elaborates further on the topics of this report.

5. Results

The field of rheumatology has changed very fast during the last decade, as biologic treatments have "revolutionized" research and what constitutes ideal treatment. Overall, desk research yielded valuable information on reimbursement conditions, clinical guidelines, physician density, and published cohort and registry studies. It should be noted, however, that the information from the desk research was at times outdated and/or inadequate. In these instances, for example patient pathways, the reported information is based on interviews instead. At times desk research and interviews have given different results, which is highlighted throughout the report in the comparisons to EULAR recommendations and in the country specific annex reports.

5.1 General findings

RA has yet to be recognized as a public health priority by Latin American countries [4]. Still, the results from this study provide some evidence that the awareness of RA is increasing in the investigated countries. The health care systems of the investigated countries are very diverse in their insurance schemes, funding and treatment pathways. Within each country, the health care system is multi-tiered, imposing differences within the countries investigated as well.

The countries investigated in this report all have different health care systems. In Brazil, 100% of the population were covered by an insurance or health plan, whereas in Mexico and Argentina, a large proportion of the patients are uninsured or have restricted coverage within their health insurance. This will, of course, have an impact of the access to RA treatment. Table 1 below presented the proportion of inhabitants covered by different types of insurance.

Table 1: Proportion of inhabitants covered by different health plans by country

	Argentina	Brazil	Mexico
Publicly insured	56%	79%	74%*
Privately insured	10%	21%	6%
Uninsured	34%**	0%	20%

*The Mexican figures are based on projections by SINAIS for 2009 as the latest real data is from 2005 and provide duplications of the insured which makes it hard to assess the proportion of patients covered by different health schemes. The quality of the healthcare received within the different public insurances differs greatly, e.g. access to innovative and high-quality healthcare is restricted when covered by Seguro Popular (29% of inhabitants)

**These have public coverage (free treatment in public hospitals) but are not covered by any insurance policy.

All the countries in the Latin American study have a regulatory body which check the quality, safety, efficacy and cost effectiveness of drugs before licensing for the local market. However, regulation of prices of drugs varies from country to country. Brazil has a cross referencing pricing mechanism whereas in Argentina, sales prices are set according to market demands but with some mechanisms that actually regulates the drug prices (e.g. by law enforcing use of generics and reference pricing for a selection of drugs). In Mexico, the price level defined by pharmaceutical companies must be obtained from the Ministry of Economics responsible for setting the price caps. There is no information regarding the time period when drugs can be accessible after regulatory approval.

Although efforts had been made in all three countries investigated to draw up local clinical practical guidelines for RA, not all were officially endorsed by the health authorities nor directly linked to reimbursement. In Brazil, the clinical protocol and therapeutical guidelines which were created in 2006 (updated in 2008) have been approved by the Secretariat for Science, Technology and Strategic Inputs (SCTIE). In Argentina, guidelines published by the Argentinean Society for Rheumatology (SAR) were neither authorized nor linked to reimbursement. Mexican College of Rheumatology has drafted national guidelines based on the American College of Rheumatology (ACR) guidelines, but these have not been officially adopted. In the absence of and in addition to national guidelines, International guidelines (EULAR and ACR) are at times followed as guidelines. Both interviews and desk research showed evidence of adherence to international guidelines in some aspects but not in other (discussed in detail later in this report).

Although therapies for RA may be formally reimbursed in many of the countries investigated, restrictions of who is eligible to prescribe, limitations of disease severity for treatment eligibility and budgets controls are used to limit the use of these therapies, especially when it comes to the more expensive biologics. Treatments for RA are, by law, fully reimbursed in Argentina under the public health care system if the patient has a disability certificate. More patients can however be covered by the will of the Obras

Sociales (OS, the Argentinean insurance fund of the working unions) or health maintenance organization (HMO) the patient belong to. In Brazil, only the three most common anti-TNFs are distributed freely to eligible patients with RA, but newer biologics are not covered. In Mexico, coverage of treatments is dependent on the insurance scheme the patient is covered by and patients may have to pay parts of the biologics themselves. Some insurance companies have started to establish formularies for drugs covered, possibly limiting future entry of new substances.

5.2 Epidemiology

It has been reported that in Latin America, RA has its onset at an average of 40 years of age, approximately 10 years earlier than in white populations in America and Europe [4]. It is, however, uncertain whether this difference is attributable to special demographic features of the inhabitants of the different regions or true differences in age presentation of RA.

Complex demographic characteristics related to ethnic background, history of colonialism and immigration patterns have notably influenced disease patterns in Latin America and the Caribbean [19]. Differences in clinical features of RA have been observed between Latin America and other regions of the world A study carried out in Columbia by Anaya et al [4, 20], found that RA is less severe in terms of x-ray documented lesions in African Latin Americans than in Columbia mestizo patients (mixed racial background, specifically denoting offspring of Spaniard and an American Indian).

Overall, prevalence is difficult to assess and studies diverge widely in their findings [21]. In addition, with better defined diagnostic criteria prevalence has decreased in the past 10-15 years, as unspecified rheumatism is excluded. As a consequence, older studies show generally a considerably higher prevalence than more recent studies. A further issue is that many studies report crude rates, or use different age groups, which makes them difficult to interpret and compare.

Data of the prevalence of RA in Latin America are scarce, although a few studies have been identified from the region. A study carried out by Spindler et al [4, 9] found prevalence of around 0.2% for patients older than 15 years in Tucúman, a city in Northwestern Argentina. Based on other studies carried out in other Latin American countries such as Brazil and Mexico which found a prevalence of 0.5% for patients older than 16 years and 0.3% respectively, a conservative prevalence rate of 0.4% can be estimated for Latin America [10-12]. As for incidence, a rate of 0.24/1000 person years have been reported for Argentina [22], although incidence is not as relevant as prevalence when it comes to a chronic progressive disease such as RA. The PANLAR/GLADAR study by the Latin American Rheumatology Associations [4], used the prevalence rate of 0.4% and took into account a female:male ratio of 8:1, which translated into a total of 1,316,903 women and 164,612 men older than 15 years of age

affected with RA in the whole region. However, other studies in the region presents a female:male ration of 3:1 [23] and 6:1[9]. Still, the data suggest that the average prevalence and age at disease onset is slightly lower in Latin America than in Europe [4]. These measurements are however correlated – a lower prevalence is seen in younger cohorts [24].

The table below shows the estimated prevalence in the adult population of RA in the three Latin American countries under study. Data on prevalence in this table have been sourced from the PANLAR/GLADAR report [4]. A female:male ration of 6:1 was assumed for Argentina [9] and 3:1 for Mexico [23]. Data on the prevalence ratio between men and women in Brazil was unavailable.

Table 2: Prevalence of RA for adult population

|	Argentina	Brazil	Mexico
Prevalence	0.2%	0.46%*	0.3%
Total number of patients	52,000	501,000	207,000
Female	44,571	-	155,250
Male	7,429	-	51,750

*The PANLAR/GLADAR study [4] rounded up the prevalence rate to 0.5% from 0.46 in the original source Senna et al [25]

Brazil has the highest reported prevalence and Argentina the lowest, although all three countries fall within a small range. Not surprisingly, Brazil also has the highest absolute number of RA patients and Argentina has the lowest. However, considering the uncertainty in some of the prevalence estimations, the difference in prevalence between countries should be interpreted with caution.

5.3   Diagnosis

Patients in the investigated countries are mainly diagnosed by RA specialists; however, GPs or other specialists (orthopaedics) may also establish the diagnosis. In Argentina, it was most common to be diagnosed by a GP. GPs and other specialists are also involved in treatment in particular in milder cases and when it comes to renewing prescriptions. The percentage of specialists in each country establishing RA diagnosis is depicted in Figure 1 below, based on the respondents in the interviews.

Figure 1: Percentage of specialists who establish diagnosis in respective country
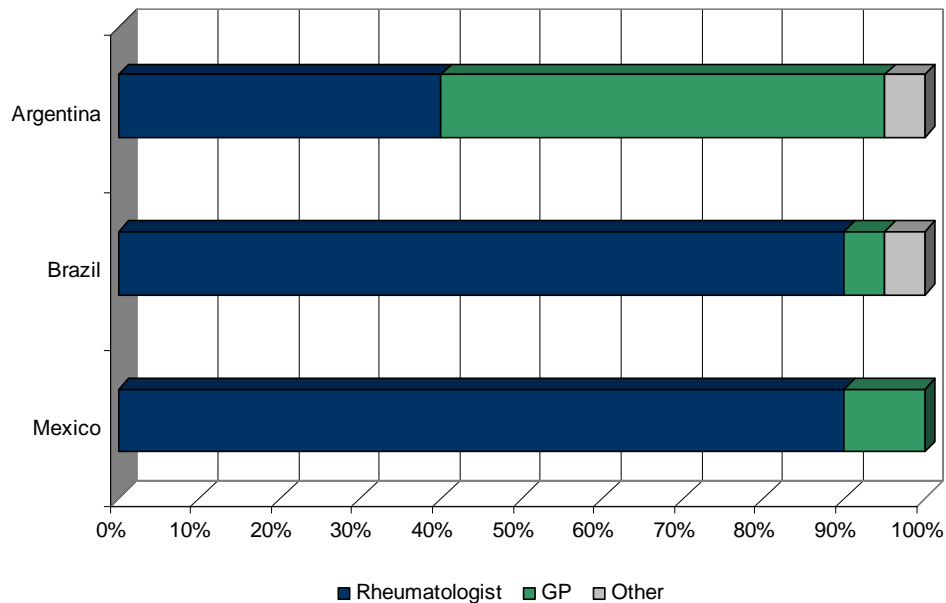
Note: the proportions are based on mean estimates obtained during interviews.

It is a commonly accepted benchmark in rheumatology that one specialist per 50,000 members of the population is required for effective diagnosis and treatment [15]. If we compare the number of rheumatologists per adults in the population – since RA is predominantly an adult-onset disease – substantial differences between countries are seen (Table 3). Argentina falls slightly above the benchmark and Brazil and Mexico exceeds it. Brazil falls below the benchmark if other specialists involved in diagnosing RA are accounted for. This has implications for the time to diagnosis and access to treatment. The results of the study of the three countries indicated that rheumatologists are mostly concentrated in larger cities. Official data on the number of rheumatologists were unavailable and the data in Table 3 below presents the estimated number of rheumatologists based on both desk research and interviews (details in country annex reports). It should also be noted that not all listed rheumatologists may be active in treating patients, but on the other hand, other specialties (such as internists) may treat RA patients instead. As for Brazil, two conflicting numbers of specialists have been reported (1,500 and 2,822, respectively), highlighting the uncertainty of these estimations.

With the new developments in treatment of RA where new tests and imaging techniques are recommended to establish the diagnosis, an attempt has also been made to investigate the availability of expensive technology such as MRI. The more expensive equipment such as MRI and power Doppler were either limited or unavailable in the public care system in the countries investigated and thereby scarcely used. Argentina had the highest number of MRIs per 1,000,000 persons (Table 3) and Mexico the lowest.

Table 3: Availability of rheumatologists and MRIs

	Argentina	Brazil	Mexico
Adult population (millions)	26	109	69
Number of rheumatologists	450	1,500*	474
Adult population per rheumatologist	58,000	73,000	146,000
MRI per 1,000,000 populations	7.2	3.6	0.26

* Another figure of 2,822 specialists (including other physicians involved in establishing RA diagnosis) yield in 39,000 adult population per specialist.

The findings in this study suggest that there is a shortage of rheumatologists which limits the access to treatment for RA patients. Access to specialists is partly explained by the time to train specialists. In Argentina and Brazil, it takes three additional years after basic medical education to become a rheumatologist. However, in Mexico, the time is up to six years (first four to be an internal medicine specialist and then another two to become a rheumatologist). Most of the specialists were also concentrated in large cities, making a difference in access between rural and urban areas in all three countries investigated.

Finally, with several biological treatments now on the market that require infusion, infusion capacity was explored in the investigated countries. However, no conclusive information at national level could be identified. Even though infusion chairs were available at local levels, some localities were unsatisfied with the numbers available. In view of the small number of interviews, quantitative numbers of infusion chairs reported in the country specific annex reports should be taken as estimates.

Table 4 shows the findings from interviews and desk research and coherence to EULAR guidelines of diagnosis. According to the EULAR guidelines, clinical examination [15] is the method of choice for detecting arthritis, associated with a minimum set of diagnostic procedures, such as complete blood cell count, transaminase analysis, urinary analysis and antinuclear antibody testing. There are further recommended procedures, e.g. chest x-ray, and blood tests for inflammation, i.e. ESR, CRP, rheumatoid factor and anti-CCP. Evidence of consistency with these guidelines were found in Argentina and Brazil but not in Mexico (some evidence of coherence to measurements but only from interviews).

In doubtful cases, ultrasound, power Doppler, and MRI may be helpful in detecting synovitis. The findings from the desk research and interviews indicated that this guideline was not followed in any of the countries examined (Table 4).

The guidelines also states that patients should be referred to a specialist ideally within 6 weeks. There was evidence of partial coherence to this guideline from Argentina and Brazil but not for Mexico. Generally, it took longer time to be referred to a specialist if in public health care systems (Brazil) and for non-severe cases (Argentina). In Mexico, rheumatologists are at third level care which means that the patient (in most cases) has

to go through first and second level care before seeing a specialist. In Argentina and Mexico, most patients have a confirmed diagnosis of RA within a year of seeking health care for RA. The same is seen for patients within the private health care system in Brazil, whereas within the public health care system where the vast majority of patients are covered, the time to diagnosis is somewhat longer (12-24 months). Because of the large proportion of patients belonging to the public health care system, the average time to diagnosis is somewhat higher in Brazil compared to Argentina and Mexico. In all countries, the disease severity of the patient is determined upon diagnosis.

Table 4: Diagnostic work-up compared with EULAR recommendations

EULAR guidance (recommendation number)	National practice consistent with EULAR recommendation?		
	Argentina	**Brazil**	**Mexico**
Patient presenting with arthritis should be referred to and seen by a rheumatologist ideally within 6 weeks of symptom onset (#1)	●	●	✘
Clinical examination for detecting arthritis may include ultrasound, power Doppler and MRI for detecting synovitis in doubtful cases (#2)	✘	✘	✘
Diagnosis requires at least the following laboratory tests: complete blood cell count, urinary analysis, transaminases and antinuclear antibodies (#3)	✓	✓	✘
Patient presenting with early arthritis should have the following factors measured: number of swollen and tender joints, ESR or CRP, level of RF and anti-CCP antibodies, and radiographic erosions (#4)	✓*	✓*	●

✓ = Yes; ✘ = No; ● = Mixed responses
✓* = Yes, but anti-CCP varying

Source: Desk research and interviews

5.4 Treatment

The PANLAR/GLADAR report (First Latin American position paper on the pharmacological treatment of rheumatoid arthritis [4]) sets forth recommendations for the management of RA. RA treatment should include an adequate balance of physical therapy, medications, rest and education. The report is from 2006 and since then more biologics have received market approval. A list of the currently available biologics in Latin America is presented in Table 5.

Table 5: Biologics available in Latin America

Biologics	Brand name	Mode of action
adalimumab	Humira®	anti-TNF
etanercept	Enbrel®	anti-TNF
infliximab	Remicade®	anti-TNF
abatacept	Orencia®	Immune suppression
rituximab	MabThera/Rituxan®	Anti CD20 B-cell
tocilizumab	RoActemra ®	IL-6 receptor antibody

5.4.1   DMARDs

The EULAR recommendations (recommendation number 5) state that treatment with DMARDs should be started as early as possible in patients with active disease, reflecting the change in patient management that came about in the 1990s. Previously, most patients were initially treated with NSAIDs. Although this recommendation does not explicitly specify that initiation should be with a small-molecule DMARD, the presence of an additional recommendation (number 9) that methotrexate should be considered the anchor drug for initial use, positions the small molecule DMARDs as first-line agents. Combination therapy with two or even three classical DMARDs is frequent.

The data from the Latin American countries indicates that although clinical practice adheres to guidelines, there may be large differences within the countries (Table 6). In Brazil, it can take 1-4 years before a patient in the public health care receives a conventional DMARD whereas the time to treatment is less than 2 years (from 12 weeks) in the private system. In the Latin American countries investigated, methotrexate was considered a first-line treatment in addition to anti-malarias. According to the PANLAR and GLADAR study, the low cost of anti-malarias (mainly chloroquin) have made them the most frequently used drug in Latin America [4]. Generally, anti-malarias have a good safety and are common therapy complementing DMARDs when biologics are not affordable. Methotrexate was given as a monotherapy or in conjunction to steroids or NSAIDs. Corticosteroids were also given to a majority of patients for a short period of time to control symptoms of RA before the effect of DMARDs is achieved.

Table 6: Treatment initiation compared with EULAR recommendations

EULAR guidance (recommendation number)	National practice consistent with EULAR recommendation?		
	Argentina	Brazil	Mexico
Patients developing persistent/erosive arthritis should be started with DMARDs as early as possible (#5)	✔	✔	●
The main goal of treatment is to achieve remission. Regular monitoring of disease activity and adverse events should guide decisions on choice and changes in treatment (DMARDs and biologics) (#10)	✔	✔	●
NSAIDs should be considered in symptomatic patients (#7)	✔	✔	✔
Among DMARDs, MTX is considered the anchor drug and should be used first in patients at risk of developing persistent disease (#9)	✔	✔	✔
Systematic glucocorticoids reduce pain and swelling and should be considered as a (mainly temporary) adjunct to the DMARD strategy (#8)	✔	✔	✔

✔ = Yes; ✖ = No; ● = Mixed responses;   *Source: Desk research and interviews*

5.4.2   Biologics

Biologics are prescribed for patients with severe RA who fail to sufficiently respond to one or two DMARDs, including methotrexate. Interestingly, there are no specific recommendations on use of biologics in the EULAR guidelines. Data highlighting their potential clinical benefit, both in established and early RA, are included in the sections of text supporting general treatment recommendation number 9 (specifying MTX as the anchor drug for first-line therapy) and recommendation number 10 (specifying remission to be the goal of treatment and regular monitoring to guide therapy changes). Biologics are rarely combined amongst themselves, but in the majority of cases associated with methotrexate.

The anti-TNFs etanercept and adalimumab, and to a lesser extent infliximab, are the first line biological options in all countries motivated by efficacy and long experience as these anti-TNF agents were the first biologics to be introduced into the market. Infliximab is less frequently used in first line biological treatment in some countries due to a perception of more safety issues as well as its need to be infused. Cycling of anti-TNFs have also been the first choice for second line biological treatment in all countries, but increasingly treatments with a different mechanism of action, such as rituximab and abatacept are considered (Table 7). At third line biological treatment, there is more use

of non-TNF agents and even experimental drugs within clinical trials (omitted from Table 7) .The therapies used in each line of biological treatment are based on information retrieved from interviews. It should be noted, however, that the interviews were conducted before tocilizumab was introduced. The newly introduced treatment may serve as an additional treatment option for second or third biologic in clinical practice in the countries investigated.

Most physicians expect to establish a sufficient and durable response during the first two lines of treatments with biologics. The anti-TNFs were the treatments most often covered by health plans in the countries investigated. High out of pocket expenses associated with the newer therapies limits their use. Data, however, suggest that there are potential savings to be made by using rituximab as a second-line biologic instead of any of the current anti-TNFs [26]. There are also expectations raised during interviews in some of the investigated countries that rituximab and abatancept will be included in covered health plans in the near future, expanding the choices of treatment for the patients.

Table 7: Treatment with biologics*

	Argentina	Brazil	Mexico
First biologic	Adalimumab,Etanercept	Adalimumab,Etanercept,Infliximab	Etanercept
Second biologic	Rituximab, Infliximab Abatacept	Adalimumab, Etanercept, Infliximab, Rituximab, Abatacept	Adalimumab, Infliximab
Third biologic	Rituximab,Etanercept Abatacept	Rituximab, Etanercept Abatacept	Infliximab, Rituximab

* Agents are not listed in any priority order

5.4.3 Non-pharmacological interventions

Countries differ in their adherence to the EULAR recommendations on non-pharmacological interventions and patient education programmes (Table 8). For both these topics, EULAR provides less specific guidance than in other areas, as there is less robust evidence on the effectiveness of either intervention. The use of these supportive interventions is thus more driven by the preferences of individual physicians and patients. The PANLAR and GLADAR report highlights the need to complement standard treatment with physical therapy and education [4]. Some consistency to non-pharmaceutical interventions recommendations were seen in all countries, although inconclusive in Mexico (Table 8). There were also mixed responses from desk research and interviews of consistency to guidelines of educational programs. The findings of this

study suggest that there are some educational programs in the investigated countries but very limited and only accessible to few patients.

Table 8: Non-pharmacological treatments compared with EULAR recommendations

EULAR guidance (recommendation number)	National practice consistent with EULAR recommendation?		
	Argentina	**Brazil**	**Mexico**
Education programmes to inform patients on coping with pain disability and maintenance of work may be employed (#6)	●	●	●
Non-pharmaceutical interventions, such as dynamic exercises, occupational therapy and hydrotherapy, can be applied as treatment adjunct to pharmaceutical interventions (#11)	✓	✓	●

✓ = Yes; ✘ = No; ● = Mixed responses   *Source: Desk research and interviews*

5.4.4   *Treatment monitoring*

EULAR recommends that disease activity is assessed at 1–3-month intervals and that structural damage is assessed every 6–12 months. These assessments include clinical examination, determination of inflammatory markers and, for structural damage, radiographs of the hands and feet. Table 9 compares clinical practice to these guidelines in the investigated countries.

The study found that Argentinean national practice was consistent with this guideline whereas the responses were mixed for Mexico. There were also regional differences where patients in rural areas were less likely to be monitored in line with the guidelines. The study found that Brazil did not adhere to these guidelines albeit some evidence of adherence was detected, only RA patients under the private system are likely to be monitored every three months. In contrast, there are difficulties in the public system to monitor every three months as recommended due to the insufficient number of outpatient visits.

Table 9: Monitoring compared to EULAR recommendations

EULAR guidance (recommendation number)	National practice consistent with EULAR recommendation?		
	Argentina	**Brazil**	**Mexico**
Monitoring disease activity should include tender and swollen joint count, ESR and CRP assessment, at 1–3-month intervals (#12)	✓	✘	●
Structural damage should be assessed by X-ray every 6– 12 months; functional assessment can be used to complement disease activity and structural damage monitoring (#12)	✓	✘	●

✓ = Yes; ✘ = No; ● = Mixed responses *Source: Desk research and interviews*
Note: The specific wording of the recommendations has been shortened in some instances for editorial reasons

5.4.5 *Factors influencing treatment choice*

Many factors affect the general access to RA treatment, but this study has also identified a few factors that may influence the choice of treatment regimen. These range from structural constraints to individual preferences, that needs to be highlighted in order to understand what factors can be affected to increase general treatment access or expand access to new treatment regimens. In summary, the factors influencing the treatment choice include:

♦ Guidelines recommending specific products or reimbursement only for a selection of treatment alternatives.

♦ Budget constraints or limitations of eligibility to prescribe RA specific drugs, which will make it less likely to be prescribed a biological treatment.

♦ Experience by the treating physician. For specialists this may be based on treatment experience or any other specific bias for a particular brand and for GPs, who generally had less experience of RA treatments, the choice is less likely to be biologics or methotrexate.

♦ Preferring ambulatory application rather than infusion at the hospital or special centre

♦ Preferring weekly rather than biweekly administration

6. Discussion

This study has investigated the difference between clinical practice and EULAR guidelines in the treatment and management of RA in order to identify the main barriers to access to treatment in the three Latin American countries (Argentina, Brazil and Mexico). The results are based on extensive desk research and interviews. The desk research has revealed data gaps in the countries investigated and therefore interviews have provided useful insight on the topics where desk research fell short. Still, the relatively small number of interviews conducted and the representativeness of respondents must be considered and study results should therefore be interpreted with some caution.

This study has noted that not all the countries had their own local guidelines. Only Brazil has official national guidelines and Argentina and Mexico have drafted national guidelines but these have not been officially adopted. Still, both interviews and desk research showed some evidence of adherence to the EULAR guidelines. The most significant differences between guidelines and practice relate to:

♦   Diagnosis process (time to diagnosis, use of procedures)

♦   Lack of patient information and programs to enhance coping behaviour

♦   Low use of non-pharmacological interventions as adjunct to medication

♦   Monitoring of patients (timing, use of imaging)

♦   Regional differences (resources, standards)

Health care system and reimbursement

Similarities in the patterns of accessibility to treatment in Latin America have been noted. In all three countries, RA was not a priority disease included in the national health plans. RA patients under the public health system are less likely to access drugs in time and have less choice compared to RA patients under the private system. Also, patients in urban areas were more likely to have better access than patients in rural areas. Only Brazil was reported to have a definite universal public health coverage in addition to private insurance. Argentina and Mexico have multi-tier systems which are a mixture of public, social security and private health coverage. Both countries have programs aimed at covering those who do not have either private insurance or covered by employment related schemes. Still, in Mexico a significant proportion of the inhabitants remain uninsured. These differences in health insurance coverage limit access to care, including specialists, treatments and tests (e.g. MRI and anti CCP).

In countries with decentralized health care systems there is great variation in treatment patterns and standards; in particular capacity and facilities are unevenly distributed resulting in waiting time for patients in underserved regions. The absence of a national strategy plan adds to this problem as there are no initiatives to achieve a more uniform level of care across the country. Besides access to specialists there are issues with availability of MRI scanners and infusion centers. This problem was more significant in Argentina and Mexico.

In all countries, biologics were partially covered, either through a public reimbursement system or by insurance policy. Still, none of the countries had full coverage for all RA patients. One large barrier to RA treatment access is hence the lack of reimbursement for biologics for parts of the patient population. This may partly be driven by the high costs of biological treatments, which have a large impact on health care budgets. The introduction of newer biologics such as rituximab, may however have a positive impact because of the lower costs associated with the treatment. For example, based on the findings of DATASUS[2] and on the annual costs of each therapy, a study by Saggia et al [26] observed that rituximab in second line, instead of a second anti-TNF agent, could annually save the public health system (SUS) in Brazil approximately R$ 2,5 million.

Referral and diagnosis

In countries where GPs act as gatekeepers (officially or just similar pattern in clinical practice), time to diagnosis tends to be longer than in others as the GP has to refer the patient to a specialist. Lack of expertise may lead to a "watch and wait" strategy by GPs and thus precious time is lost to prevent disease progression. In all three countries investigated, GPs acted as gatekeepers before patients are referred to a specialist (in Brazil and Argentina not formally but most patients are attended by a GP at their first contact). Patient awareness is also low in all countries and patients thus present late to the GP or specialist. However, the results from this study indicate that those covered by private insurance are likely to be referred to a specialist much quicker than those under the public system.

Referral to a specialist is also limited by the identified shortage of specialists in the countries. There is a special training for rheumatologists in all countries of between 3-6 years. According to information from the interviews, specialists would require more training in imaging technologies as lack of expertise and funding issues were both mentioned as barriers to more systematic use of MRI and ultrasound.

In principle most RA patients with poor prognosis are identified from those with a better prognosis. "Severe patients" with "active disease" are treated differently, with faster referrals and faster access to biologics. ACC positivity, disease activity index and number of joints affected are some of the criteria used to identify patients with poor

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[2] DATASUS is a public database available on the internet which was used to collect the number of treatments conducted with different biologic drugs

prognosis. This could present an opportunity for targeted treatment to maximize the benefit of biological treatment.

Treatment and monitoring

Decisions on treatment depend on guidelines but also on patient characteristics. The choice of a DMARD other than methotrexate is motivated by assessment of severity or patient circumstances (pregnancy) and less severe patients are often treated with anti-malaria medication. Whilst the choice of first biologics is fairly consistent across countries the choice of further treatment options is influenced by anticipated responsiveness to anti-TNFs.

The prices for biological treatment, at a private level are affordable for only a few patients. Treatments that are not reimbursed (or reimbursed after use) are associated with high out of pocket expenses for the patients, which only few can afford. The use of reimbursed biologics is also limited through budget controls and restrictions of patient eligibility and prescription authorization. The coverage for the patients were much dependent on the health scheme the patient belonged to, with better access for patients in urban areas and/or in private health plans.

Some gaps in monitoring were identified in this study mainly due to the limited access to specialists. Information programs were also either non-existent or very limited.

7.   Conclusions

In conclusion, patients in Latin America do not receive diagnosis and treatment in a timely manner, leading to disease progression which is associated with large effects on the patient's quality of life and high costs to the society. To ensure timely and effective treatment to patients with RA, it is important that clinical guidelines and regulations controlling the flow of patients and treatments are continuously updated to reflect the most recent findings in therapies and efficient patient pathways.The main barriers to RA treatment access identified in this study can be divided into three parts, namely general access to care, access to specialist care and access to biological treatments.,

♦   General access to care

This study has identified that the access to health care is the first barrier to RA treatment. The diverse health care systems, decentralized health care and multi-tier insurance schemes have implied an uneven access to care within the investigated countries. In Argentina and Brazil, all inhabitants are covered by some sort of health insurance/plan whereas in Mexico, a significant proportion of the inhabitants are uninsured. In addition, both in Argentina and Mexico, a large proportion of the patients are covered by a health plan that only provides limited treatment access. In all countries, patients in rural areas and in public health care schemes are less likely to have access to timely care compared to those in urban areas or covered by a private insurance.

♦   Access to specialist care

The comparison of clinical practice and EULAR guidelines revealed that the average time to diagnosis were longer than the guidelines in all investigated countries. In all the countries, GPs acts as gate-keepers of care (not officially in Argentina, but most patients are first attended by their GP), this implies that the time to see a specialist is longer, and hence also effects the time to diagnosis. This study has also highlighted a lack of specialists, especially in rural areas, further increasing the time to referral. There were also a shortage of imaging facilities and where they were present, they were still rarely used for establishing diagnosis or monitoring the disease.

♦   Access to biological treatment

Anti-TNF treatments as second line treatment for RA were covered for some patients in all countries. However, other biological treatments were not, limiting the choice of treatments unless a patient can afford it themselves. Although treatments were reimbursed/covered for patients, other means were used to limit their use. These include restrictions of eligible patients, of prescription authorisation and local budget. There also seem to be a higher probability of being prescribed a biological treatment early in the course of the disease if the patient were covered by a private health insurance.

8. References

Note: The EULAR recommendations for arthritis management (Combe et al, reference 11, below) are available through the EULAR website: <u>http://www.eular.org/</u> *(accessed 12 Nov 2009)*

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