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Original article

Global prevalence of ankylosing spondylitis

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Abstract

Objectives. For effective health care provision, knowledge of disease prevalence is paramount. There has been no systematic endeavour to establish continent-based AS estimates, however, prevalence is thought to vary by country and background HLA-B27 prevalence. This study aimed to estimate AS prevalence worldwide and to calculate the expected number of cases.

Methods. A systematic literature search was conducted. Prevalence data were extracted and used to calculate the mean prevalence by continent and the expected number of cases based on country-specific prevalence (or, if missing, the prevalence from neighbouring countries). A second estimate was made using the prevalence from countries with similar HLA-B27 prevalences if a country-specific prevalence estimate was not available.

Results. The mean AS prevalence per 10 000 (from 36 eligible studies) was 23.8 in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America and 7.4 in Africa. Additional estimates, weighted by study size, were calculated as 18.6, 18.0 and 12.2 for Europe, Asia and Latin America, respectively. There were sufficient studies to estimate the number of cases in Europe and Asia, calculated to be 1.30–1.56 million and 4.63–4.98 million, respectively.

Conclusion. This study represents the first systematic attempt to collate estimates of AS prevalence into a single continent-based estimate. In addition, the number of expected cases in Europe and Asia was estimated. Through reviewing the current literature, it is apparent that the continuing conduct of epidemiological studies of AS prevalence is of great importance, particularly as diagnostic capabilities improve and with the recent development of the criteria for axial SpA.

Key words: ankylosing spondylitis, spondyloarthropathies, prevalence, epidemiology, systematic review.

CLINICAL SCIENCE

Introduction

AS is an inflammatory arthritis within a family of related disorders (SpA) including PsA, reactive arthritis, SpA associated with IBD and uSpA. These SpAs exhibit a similar genetic background, clinical features and symptoms. The prognosis for patients with AS is variable and is determined, in part, by the presence of a number of extraspinal manifestations (such as uveitis, psoriasis and IBD), the age at diagnosis and the treatment provided [1, 2]. Generally AS results in serious impairment of spinal mobility and physical function, which has an impact on quality of life.

AS usually initially presents during the third decade of life, and rarely after the age of 45 years. The prevalence of AS is generally believed to be between 0.1% and 1.4% globally, although it is difficult to be certain, as few prevalence studies have been conducted compared with other rheumatic disorders such as RA [3]. In addition, to date there have been no systematic attempts to collate data from the available studies of AS prevalence. The disease is thought to exhibit a higher prevalence among those of lower socioeconomic status, who are also more likely to have poor functional outcomes [4–6]. Reviews have highlighted the global variation in the background prevalence of the known AS risk allele HLA-B27 [7, 8] and, as 90% of AS patients exhibit this variant, there is also likely to be geographical differences in disease prevalence. Additionally there is some gender disparity within AS,

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with reported gender ratios of around 2:1 (male:female), although this estimate has also been shown to vary considerably between studies and across time [4, 9].

For the effective provision of health care, knowledge of disease prevalence is paramount, therefore this study aims to determine the global prevalence and gender ratio of AS by collating studies for each world region. In addition, the total estimated number of cases within the continents will be estimated where sufficient numbers of studies of AS prevalence are available.

Methods

Information sources

A systematic literature search was conducted using a set of pertinent MeSH terms (mt) and text words (tw). The search string {[AS (mt) OR Spondyloarthropathies (mt) OR Spondylarthropathies (tw) OR Spondylitis (mt) OR Musculoskeletal diseases (mt) OR Rheumatic diseases (mt) OR Spinal diseases (mt)] AND [Prevalence (mt)]} was applied to the Medline, Embase, CINAHL, AMED and Web of Science databases on 17 May 2012. The search string was also limited to English and Human, but not by date.

Eligibility criteria

Studies were considered eligible if the following criteria were met: (i) case ascertainment was facilitated through the use of the New York and modified New York criteria [10], clinical diagnosis or by rheumatologist opinion; (ii) the study used a sampling frame that could be considered population-based with respect to the adult population and would allow a population-based estimate of prevalence to be determined and (iii) the prevalence of AS was reported, or sufficient data were present to calculate this. Studies restricted to indigenous populations were excluded from the review as not being representative of a country's population. Here, indigenous populations are defined as communities, often native to the country, whose cultural and societal identities are distinct from those of the national population.

Study selection

Potential papers were screened for relevance, initially by title, following which abstracts of the selected articles were reviewed independently by two authors. To ensure that no eligible studies were discarded, in the case of disagreement, the article in question was accepted for review at the full paper stage if either reviewer considered it to be potentially eligible. The full texts of all selected articles were read by two readers, independently, and where there was uncertainty over eligibility, this was discussed and a consensus reached. The reference list for each study was also screened to identify additional papers that may have been missed during the original search.

Data extraction

The information extracted was (i) country of study, (ii) size of study population, (iii) prevalence (with 95% CI) and (iv) gender ratio. The latter two were computed if they were not presented explicitly in the paper but sufficient information was presented such that they were calculable. Prevalence estimates standardized to the relevant national population were preferentially used if present; however, if absent, crude prevalence estimates and exact binomial CIs were calculated. Extraction was conducted by both independent readers and entered into independent tables. Both sets of extracted data were subsequently compared to determine levels of agreement.

Calculating the number of persons with AS

Where sufficient data existed, the number of persons with AS within a continent was estimated using recent population census data (www.who.int/en/) and the available country-specific prevalence. Europe was defined for this analysis as including all countries within the mainland continent, West of and including Russia and Turkey. In addition, the island nations of Iceland, Malta, Cyprus, Ireland and the UK were also included.

Asia was defined as all mainland countries East of and including Kazakhstan and Syria, but excluding Russia and Turkey. In addition, the islands of Japan, Taiwan, Philippines, Indonesia, Maldives and Sri Lanka were also included. Sufficient data was defined as the prevalence of AS being reported from five or more countries within a continent and a combined study population $>50\,000$. If country-specific prevalence was not available, the absolute number of persons with AS was calculated using two approaches. First, the prevalence from neighbouring countries was used or, if multiple neighbouring estimates were available, the prevalence reported from the largest study sample. Conversely, if no prevalence was available from a neighbouring country, that from the closest study (geographically) was used. A second estimate was made, as above, but where country-specific prevalence was missing, the prevalence from countries (within the same continent) with the most similar HLA-B27 prevalence was used. The background prevalence of HLA-B27 was ascertained through published gene frequencies [11]. In addition to calculating the number of AS patients in a continent (where sufficient data existed), the mean and weighted mean prevalence of AS (weighted by the size of the study sample from which the estimates were derived) within Europe, Asia, Africa, North America and Latin America were calculated.

Results

A total of 5024 articles were identified using the keyword search, of which 361 were considered to be potentially relevant on the basis of title. After duplicate studies were removed, 253 articles remained, of which 111 were subsequently discarded as being not relevant to this review (determined from the abstract). Of the remaining studies, 51 were review articles, 37 contained insufficient data to determine prevalence, 9 studied AS prevalence within indigenous populations, 10 were multiple publications from studies already included and 3 could not be traced. Thus a total of 32 studies were shown to be eligible for inclusion at the final stage, and a further four

papers were identified through cited references (supplementary Fig. S1, available at *Rheumatology* Online). Among these studies, 14 used population samples from Europe, 15 from Asia, 4 from Latin America, 2 from North America and 1 from South Africa (Table 1). In addition, 16 of these studies also reported an AS gender ratio.

Study design

The majority of studies (29/36) used a population-based cross-sectional design, during which AS cases were identified through an initial screening questionnaire and subsequent examination of positive responders. The remaining studies used hospital/clinic-based records to determine the number of AS patients within a given catchment area. Due to these methodological differences, the latter studies are presented separately (Table 2) and were not included in the prevalence estimates or the calculation of the number of AS patients within each continent.

Prevalence of AS in Europe

The prevalence of AS was presented by 14 European studies, 5 of which were based on hospital/clinic studies and

Table 1 Prevalence of AS grouped by country and continent

Prevalence of AS (population-based studies)					
Continent/country	**Study size**	**Cases, *n***	**Diagnostic method**	**Prevalence, per 10 000**	**95% CI**
Europe					
France [12]	9395	14	Clinical	14.9[a]	8.9, 24.9
Finland [13]	7217	11	Clinical	15.0	8.0, 27.0
Greece [14, 15][b]	1705	5	Clinical	29.3[a]	12.5, 68.5
	8740	19	mNY	24.0	16.0, 32.0
Hungary [16]	6469	15	NY	23.2[a]	14.1, 38.2
Italy [17]	2155	8	mNY	37.0	23.0, 49.0
Lithuania [18]	4244	4	Clinical	9.4[a]	3.7, 24.2
Turkey [19, 20][b]	2835	14	mNY	49.0	26.0, 85.0
	17 835	15	Rome	11.9	11.3, 12.5
Mean = 23.8 per 10 000					
Weighted mean = 18.6 per 10 000					
Asia					
Bangladesh [21]	5160	3	Clinical	5.8[a]	1.9, 17.1
Philippines [22]	3006	1	ACR	3.0	0.0, 10.0
Pakistan [23]	4232	2	Clinical	4.7[a]	1.3, 17.2
India [24, 25][b]	8145	5	Clinical	7.0	4.0, 12.0
	4092	4	Clinical	9.8[a]	3.8, 25.1
Malaysia [26]	2954	4	Clinical	24.3[a]	11.3, 51.9
Vietnam [27]	2119	1	Clinical	4.7[a]	0.8, 26.7
China [28–32][b]	2040	4	mNY	19.6[a]	7.6, 50.3
	6584	8	mNY	11.0	3.0, 19.0
	4192	13	Clinical	26.0	11.0, 42.0
	5057	13		26.0	14.0, 40.0
	10 921	29	mNY	25.3	15.9, 34.7
	5922	22	NY	37.1[a]	24.5, 56.2
Iran [33]	10 291	12	Clinical	11.7[a]	6.7, 20.4
Taiwan [34]	8998	15	NY	33.7[a]	23.6, 47.9
Mean = 16.7 per 10 000					
Weighted mean = 18.0 per 10 000					
Latin America					
Cuba [35]	3155	6	Clinical	19.0	8.0, 40.0
Mexico [36–38][b]	19 213	—	mNY	15.0	9.0, 20.0
	3915	1	mNY	2.6[a]	0.5, 14.5
	4713	2	mNY	4.2[a]	1.2, 15.5
Mean = 10.2 per 10 000					
Weighted mean = 12.2 per 10 000					
North America					
USA [39]	4688	15	Clinical	31.9[a]	19.4, 52.7
Africa					
South Africa [40]	1352	1	Clinical	7.4	1.3, 41.8

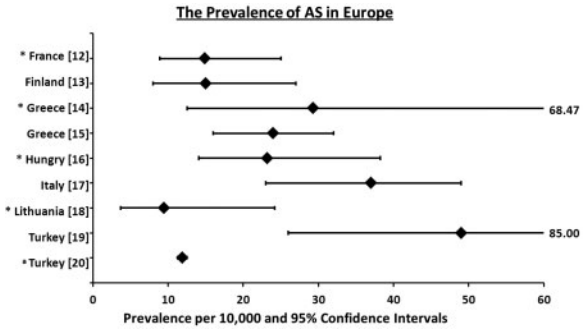
[a]Prevalence calculated by hand with exact binomial CI. [b]Mean prevalence across studies within the same country used to calculate the mean prevalence of the continent. mNY: modified New York criteria; NY: New York criteria.

Table 2 Hospital/clinic-based AS prevalence studies

Prevalence of AS (hospital-based studies)					
Country	**Study size**	**Cases, *n***	**Diagnostic method**	**Prevalence, per 10 000)**	**95% CI**
Czech Republic [41]	154 374	185	Clinical	11.9[a]	10.38, 13.84
Greece [42]	448 435	113	mNY	2.9	2.6, 3.3
Iceland [43]	220 441	280	mNY	10.4	9.1, 11.7
Norway [44]	217 000	570	mNY	26.3[a]	24.2, 28.5
Sweden [45]	849 253	746	Clinical	8.8[a]	8.2, 9.4
Japan [46]	101 100 000	6 760	Rome or NY	0.7[a]	0.65, 0.68
USA [47]	52 000	68	Various	13.1[a]	10.3, 16.6

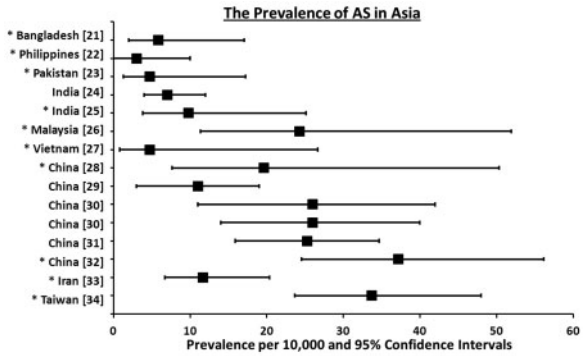
[a]Prevalence calculated by hand with exact binomial CI. mNY: modified New York criteria; NY: New York criteria.

Fig. 1 Prevalence of AS in European countries based on population studies



*Prevalence and exact binomial CI calculated.

Fig. 2 Prevalence of AS in Asian countries based on population studies



*Prevalence and exact binomial CI calculated.

excluded from mean prevalence calculations (Table 2). Study size ranged from 154 374 [41] to 849 253 [45], while reported prevalence ranged between 2.9 and 26.3 per 10 000 [42, 44]. The remaining studies, all cross-sectional, ranged in size from 1705 to 17 835 [14, 20] (total study population 60 595) and the prevalence reported ranged between 9.4 and 49.0 per 10 000 [18, 19] (Table 1 and Fig. 1). The mean prevalence of AS was calculated as 23.8 per 10 000 (weighted mean of 18.6) for the entire continent. Studies based on clinical diagnosis reported lower prevalence estimates (mean 17.2, weighted mean 15.0 per 10 000) in contrast to those using either the New York or modified New York criteria (mean 33.3 and weighted mean 28.6 per 10 000).

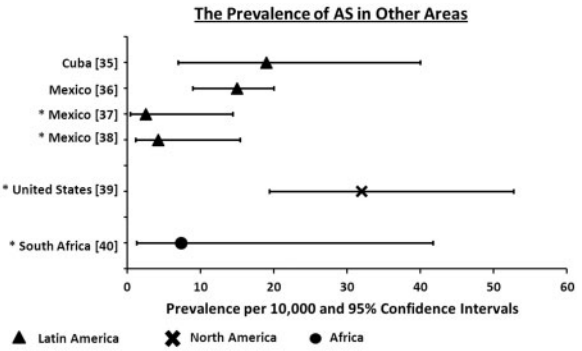
Prevalence of AS in Asia

Within Asia, the prevalence of AS was reported by 15 studies, only 1 of which was determined to be a hospital-based study [46]. The remaining 14 studies reported AS prevalence between 3.0 and 37.1 per 10 000 [22, 32] (Table 1 and Fig. 2) and individual study size ranged between 2040 and 10 921 [28, 31] (total study population 83 353). The mean prevalence of AS within Asia was 16.7 per 10 000 (weighted mean 18.0 per 10 000). South Asian countries provided the lowest prevalence estimates, between 3.0 and 24.3 per 10 000 [22, 26] (mean 8.5, weighted mean 7.8 per 10 000), whereas East Asian countries exhibited varied prevalences from 11.0 to 37.1 per 10 000 [29, 32] (mean 25.5, weighted mean 26.4 per 10 000). Lastly, the only study from West Asia (Iran) reported an AS prevalence of 11.7 per 10 000, although it reported some variances due to ethnicity: 11.0 and 15.0 per 10 000 among Caucasians and Turks, respectively [33]. As within Europe, Asian studies based on a clinical diagnosis reported a lower prevalence (mean 13.3, weighted mean 12.7 per 10 000) compared with those using either the New York or modified New York criteria (mean 25.3, weighted mean 26.5 per 10 000). The only hospital-based study within Asia reported the lowest AS prevalence of any study found within this review (0.7 per 10 000) [46].

Prevalence of AS in the Americas

The prevalence of AS in North America was reported by two studies implementing different study designs. The prevalence estimates were 13.1 per 10 000 [47] (hospital-based study) and 31.9 per 10 000 [39] (cross-sectional study) (Tables 1 and 2 and Fig. 3). All four

Fig. 3 Prevalence of AS in other continents based on population studies



*Prevalence and exact binomial CI calculated.

Latin American studies (total study population 30 996 individuals) used a cross-sectional study design and reported prevalence estimates between 2.6 and 19.0 cases per 10 000 [35–38].

Prevalence of AS in Africa

A single eligible South African study of 1352 persons (cross-sectional design) reported the prevalence of AS within Africa to be 7.4 per 10 000 [40] (Table 1 and Fig. 3).

Gender ratio in AS

Thirteen cross-sectional studies reported the ratio of male to female cases (Table 3); this ranged between 1.2 and 7.0:1 [17, 19] (mean 3.4:1). There were some differences in the estimated gender ratios between countries, but notable consistency between the mean estimates within each continent. By continent, the mean gender ratio was 3.8:1 in Europe and 2.3:1 in Asia.

The estimated number of AS cases in Europe and Asia

There were sufficient numbers of studies available within Europe and Asia and involving sufficiently large populations to estimate the number of cases of AS within these continents. Using country-specific census data and the prevalence data available for each country, or neighbouring country, the number of AS patients in Europe was calculated to be 1.30 million. The alternate method of computing the number of cases for countries without a prevalence study, using the prevalence estimate of the country with the most similar estimated HLA-B27 prevalence, yielded an estimate of 1.56 million individuals. The mean across both methods was 1.43 million. Within Asia, the first calculation method estimated the number of AS patients to be 1.53, 3.15 and 0.29 million within South, East and West Asia, respectively, the sum for the entire continent being 4.98 million. The second method yielded estimates of 1.40, 2.96 and 0.28 million for South, East and West Asia, respectively, with a sum of 4.63 million. The mean across both calculation methods was computed to be 4.81 million for the entire continent (1.46 million in the South, 3.05 million in the East, 0.28 million in the West).

Table 3 Gender ratio of AS

Gender ratio in AS			
Continent	Country	Ratio (male:female)	Continent mean
Europe	Finland [13]	2.7	3.8
	Greece [14, 42]	4.0	
		6.1	
	Italy [17]	7.0	
	Norway [48]	3.1	
	Turkey [19, 20]	1.2	
		2.8	
Asia	China [31, 32]	4.5	2.3
		1.7	
	Iran [33]	1.4	
	Taiwan [34]	1.5	
North America	USA [39]	6.0	n/a
Latin America	Cuba [35]	2.0	n/a

Discussion

There are important differences between the prevalence of AS across continents but some consistency in reported prevalence within these regions. AS is more common within Europe (mean 23.8, weighted mean 18.6 per 10 000) and Asia (mean 16.7, weighted mean 18.0 per 10 000) than within Latin America (10.2, weighted mean 12.2 per 10 000). Single studies from North America and Africa reported the prevalence of AS to be 31.9 and 7.4 per 10 000, respectively. In addition, the estimated number of AS cases ranges from 1.30 to 1.56 million in Europe and 4.63 to 4.98 million in Asia. The mean gender ratio across all studies is 3.4:1 (males:females).

Although we conducted a literature review in order to identify all published articles pertaining to the prevalence of AS, the search strategy employed may have limitations. During the literature review the search results were confined to those papers published in English, which may have excluded potentially eligible papers published in other languages. AS prevalence has been previously reported as 5–20 per 10 000 in Europe, 19–54 in Asia, 10–15 in North America and 0–8 in Africa [9, 49]. Although the mean values presented here largely fall within the ranges previously reported, there are some differences. These may be largely due to the strict inclusion criteria employed here. Several studies that have been included within other reviews have been excluded here since they did not fulfil the required criteria. This mainly related to criteria that were deemed important in terms of case ascertainment and the ability to provide a population-based prevalence estimate. Because of these rigorous inclusion criteria, we are confident that the prevalences presented here represent the most accurate estimates possible using the available data.

In addition to limitations in the search strategy, there may be variations between the articles identified within this review. While the majority of studies implemented a cross-sectional design, others used hospital-based designs, using clinic records to identify AS cases, both of which have limitations. Cross-sectional designs require the active participation of subjects. However, this design does facilitate the consistent application of classification criteria. Hospital-based study estimates rely on accurate recording within medical records, referral of the patient to the clinic and the application of uncertain diagnostic criteria. In addition, the latter design can only include previously diagnosed cases. Due to the fundamental differences in designs and the basis of their estimates, those with record-based case ascertainment were excluded from all further analysis. Although not included in the estimates of the number of cases and prevalence, these studies provide valuable information regarding AS prevalence. While the prevalence estimates reported from the hospital-based studies generally fell within the range reported among the cross-sectional designs (with the notable exception of Japan), the study populations within the former were much larger.

There were also differences in the methods employed during case ascertainment. Among the articles identified, the majority of studies utilized either the New York or modified New York criteria [10] to identify AS cases, or via clinical diagnosis. The prevalence estimates using clinical diagnosis were consistently lower than those using the validated criteria, which makes prevalence comparisons between countries difficult. Furthermore, the development of different diagnostic techniques may make combining results from different time periods problematic. As an example, we excluded from this review (due to not having a population-based study sample) a study originating from Germany that presented a particularly high AS prevalence (55 per 10 000) [7]. This study was the only one identified that used MRI scanning during diagnosis, suggesting that estimated prevalence may be highly dependent on the method of diagnosis used. This is supported by further findings that indicate the median prevalence reported from studies using clinical diagnosis is consistently lower than those using New York or modified New York criteria. The issue of classification is of particular relevance due to the recent development of new criteria for the classification of axial SpA [50]. The new criterion, published by the Assessment of SpondyloArthritis international Society (ASAS), is the first to incorporate MRI scanning to aid in the detection of non-radiographic SpA. As criteria such as this gain wider acceptance within the field, case detection and time to diagnosis will inevitably improve. This in turn raises the possibility that future estimates, which may be able to include non-radiographic SpA in addition to AS, will be higher than the estimates reported here and may reflect more closely the findings of the German study.

In addition to country variation, a Taiwanese study indicated that there may be geographical differences in the prevalence of AS [34]. The study reported that while both urban and rural areas reported similar AS prevalences (calculated to be 20.1 and 20.0 per 10 000), the suburban population prevalence was much lower (10.0 per 10 000). Although the overall country estimate was used for this review, the study sample was evenly distributed between the rural, suburban and urban areas and as such may not accurately represent the population distribution of Taiwan. This may also indicate that the differences in prevalence between countries may be partly due to inherent heterogeneity within these countries with respect to the urban/rural divide, socioeconomic status and genetic variation.

In 2008 an attempt was made to estimate the total number of individuals affected by a number of arthritic conditions within the USA [51]. Although the authors were not able to estimate the number of persons with AS (due to the lack of available studies), the numbers with SpA were estimated at between 0.6 and 2.4 million adults. Using this literature review, we have attempted to present an estimate of the number of AS cases within Europe and Asia. To determine how robust these calculations were to different assumptions and to reflect population variation of the risk allele HLA-B27, the calculations were performed using two methods. The resulting European and Asian estimates showed remarkable consistency [1.30–1.56 million (Europe) and 4.63–4.98 million (Asia)]. This study also brings together for the first time the available population data regarding the gender ratio in AS and shows some variation between countries, often diverging from the 2:1 (male:female) ratio often quoted in the literature [4, 9]. Within the current study there is no evidence to suggest that this ratio varies significantly by continent.

Conclusions

Previous AS prevalence estimates have varied considerably between studies, which is apparent in the wide range reported within the literature. This review provides a single median AS prevalence estimate for each of the major global continents (from which there were sufficient prevalence data) calculated from the individual studies published from that area. In addition, we present the first estimate of the number of AS cases in Europe and Asia. Despite differences in study design, sampling frame and case ascertainment methods employed, the studies presented here have shown relatively consistent prevalence rates and gender ratios within the continents studied, despite previous assumptions that these may vary. The continuing conduct of epidemiological studies within this area is of great importance, since as classification criteria change and technologies such as MRI scanning become more widely used, future prevalence studies may be able to incorporate non-radiographic SpA as well as AS and are likely to report higher rates than have been published thus far.

Rheumatology key messages

- This is the first systematic attempt to collate available AS prevalence estimates by continent.
- The number of AS cases is estimated at 1.30–1.56 million in Europe and 4.63–4.98 million in Asia.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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