Adherence to guidelines in use of biological agents to treat psoriasis in Brazil

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TITLE: Adherence to guidelines in use of biological agents to treat psoriasis in Brazil

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[BACKGROUND]: In São Paulo, Brazil, patients gain funding for biological agents for treatment of psoriasis through lawsuits to the government. The extent to which management of such patients adhere to authoritative guidelines is uncertain.

[OBJECTIVE]: To determine the extent to which clinical practice adheres to authoritative guidelines in patients receiving treatment for psoriasis through lawsuits.

[METHODS]: We identified patients through records of the State Health Secretariat of São Paulo from 2004 to 2011. We consulted guidelines from five countries and chose as standards only those recommendations that the guidelines uniformly endorsed. Pharmacy records provided data regarding biologic use. Guidelines recommended biologics agents only in patients with severe psoriasis who have failed to respond to both topical and systemic therapies (e.g. cyclosporine and methotrexate) and recommended yearly monitoring of blood counts and liver function.

[RESULTS]: Of 218 patients identified in the database, 3 did not meet eligibility criteria and 12 declined participation. Of 203 patients interviewed, 91 were still using biological medicine; we established adherence to laboratory monitoring in these patients. In the total sample, management failed to meet standards of prior use of topical and systemic medication in 169 (83.2%) of the patients. .Of the 91 patient using biological medicine at the time of the survey, 23 (25.2%) did not undergo appropriate laboratory tests.

[CONCLUSIONS]: Important discrepancies exist between clinical practice and the recommendations of guidelines the management of plaintiffs using biologic drugs to treat psoriasis.

Strengths and limitations

Strengths

- We obtained a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis.
- We contacted and obtained consent from 203 of 218 potentially eligible patients.
- Pharmacy records of medication use and corroborating information from patient interviews ensured accuracy.
- Duplicate review of interview recordings ensured accurate information.
- We surveyed a number of key guidelines including both public agencies and specialty societies from a number of countries and used as criteria only recommendations included in all the guidelines.

Limitations

- Patients' memory of prior medication use may not have been accurate.
- We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents.

INTRODUCTION

Psoriasis, chronic inflammatory immune-mediated skin disease that predominantly affects the skin and joints[1] occurs in between 1.5 to 3% of the population[2]. Onset may occur at any age but peaks in the second and third decades. The severity of psoriasis varies widely, and its course is characterized by relapses and remissions, though it usually persists throughout life. Its negative impact on health-related quality of life is similar to that of ischemic heart disease, diabetes, depression and cancer and severe psoriasis is associated with an increase in mortality [3].

The significant reduction in quality of life and the psychosocial disability suffered by patients highlight the need for prompt, effective treatment, and long-term disease control[4 5]. In mild psoriasis, topical treatment can be effective[6]. Those with moderate to severe disease often require treatment with phototherapy and systemic treatment[7]. When systemic traditional treatment with cyclosporine, methotrexate, or acitretin fail (non-biologic systemic agents or N-BISYS), systemic biological therapies such as the tumor necrosis factor antagonists' adalimumab, etanercept and infliximab, and the monoclonal antibody ustekimumab that targets interleukin-12 (IL-12) and IL-23 become options.[7-10].

Due to their immunosuppressive activity, some anti-TNFs have been associated with a small increased risk of infection in patients with psoriasis[11], and studies of TNF antagonist use in other disease areas have raised concerns over a potential link to cardiovascular side-effects, malignancies, and neurological defects[11-13]. Guidelines uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents.

In Brazil patients can, once they are prescribed by a clinician, go to the courts to force the state to pay for expensive medication such as biologics. Court decisions may not be consistent with optimal standards of care in terms of patients who are appropriate for use of biologics. Furthermore, once patients receive biologics through court decisions, subsequent management may not be optimal.

The objective of this study was to identify standards of management of psoriasis common to major international guidelines and to evaluate the extent to which Brazilian physicians who prescribed biologics that courts approved on the basis of law suits adhered to these standards.

METHODS

The protocol was authorized by the State Department of Health (SES-SP) and also approved by the ethics committee for clinical research of University of Sorocaba on August 17, 2009, with protocol number 011/2009.

Choice of Guidelines and Guideline Recommendations

We consulted guidelines from the following countries: United Kingdom[14], Germany[8], Brazil,[10] United States and Canada.[15] We used both national guidelines (NICE, SIGN)[6 7] and specialty society guidelines. We reviewed all recommendations in each guideline and chose as standards only those recommendations that were uniformly endorsed across all guidelines.

Recommendations uniformly endorsed by every guideline[6-10]specified that biologics should only be used in patients with severe psoriasis who had failed to respond to, have a contraindication to, or are intolerant of topical therapies, and at least one systemic therapy (e.g. cyclosporine or methotrexate). Guidelines also uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents and also to evaluate control of psoriasis. Guidelines specified that the review should include monitoring of complete blood cell count and liver function tests.

Eligibility Criteria

Patients were eligible if they had, through lawsuits filed against the state of São Paulo in the period 2004-2010, gained access to biologics for treatment of psoriasis. All patients gave informed consent.

Identification of Patients and Collection of Patient Data

In order to identify eligible patients, two researchers abstracted data from all the dispensing orders in the database for psoriasis - identified by ICD code L40 - originating from lawsuits from 2004-2010 including the name, address and telephone number, gender, age, healthcare provider, whether that provider worked in the public or private system, type of biologic d ispensed, and diagnoses.

We contacted patients with psoriasis by telephone, and if they proved eligible and agreed to participate in the study, conducted interviews. The interviews were conducted by telephone using Computer Assisted Telephonic Interviews (ITAC) technology with a microcomputer handset with headphones. This system allows recording and monitoring of the duration of the conversation [16 17]. Research staff working in pairs independently recorded data from the interviews, with discrepancies resolved by the principle investigator (LL).

The interview schedule was developed in consultation with a local dermatologist (see **Appendix)** after consideration of the recommendations consistent across guidelines. An electronic form was developed in Microsoft Office Access based on the instrument developed for the interviews. To address the items listed in the instrument, 16 screens were designed to record the data from the interviews. Each interviewer received training on use of language related to each question in the interview schedule. The questionnaire included the following: what drugs the patient was using for the treatment of psoriasis prior to the court judgment, the time of diagnosis of psoriasis, and whether patients received at least annual review. For patients still taking biologics we determined if they had received a medical consultation in the previous year and what tests had been undertaken in the previous year. In Brazil, patients receive records of all their laboratory tests and typically retain these records indefinitely; all patients still receiving biologics reported that they had retained records of all of laboratory tests undertaken during the previous year.

Patients' report of the period in which they used the biologics were cross-checked with data obtained from pharmacy records and from legal records form lawsuits. Legal records form lawsuits gave us the name of patients, name of the drugs obtained through the law suit, whether the prescription came from private or public insurance, sex and age of patients. If we found discrepancy between the three sources of information, we considered the information from pharmacy records definitive. Thus, definitive information about the name of the biologic and the duration of use of the biologic was obtained from the pharmacy, and definitive information of the time of diagnosis, use of previous medicines, and laboratory results was obtained from the patient. We considered guideline adherence adequate when court decisions and subsequent clinical care had adhered to all recommendations from guidelines.

In the interviews we also asked patients about their adverse effects and whether these led to discontinuing medications and their perception of the effectiveness of the biologic agents.

RESULTS

We reviewed 25,184 lawsuits that had succeeded in obtaining medicines, dietary supplements, or other health products, such as orthotics and prosthetics, and diagnostic and therapeutic procedures in the period deposited in the Public Finance Courts Capital in period 2004 to 2010. Of 218 patients identified as using biologics for psoriasis, in 3 the contact information was a law office that did not allow us to contact patients, 1 patient had died, 2 had never used the biologic that was mandated by the court decision, and 9 refused the interview. We interviewed 203 patients, of whom 91 (44.8%) were still using a biologic agent (Figure 1).

Eligible patients received one of four biologic drugs: adalimumab, etanercept, infliximab. Table 1 presents the socio demographic and medical health characteristics of the 203 eligible patients as well as the duration patients used the biologic agents granted payment by the courts. Over a third of the patients used the biologic agents for less than a year, and over 50% for 1 to 3 years.

Table 1 - Baseline characteristics of plaintiffs with psoriasis

	Patients N=203	%
City of residence		
São Paulo	122	60
Other	81	40
Health care		
Private	141	69.5
Sex		
Male	*129*	*63.5*
Age (years)		
19 - 59	156	76.9
≥ 60	47	23.1
mean ± sd		48.9 ± 13.7
Time of diagnosis (years previous)		
6 or more	177	84.9
2 - 5	25	10.2
≥ 1 year	1	0.5
Comorbidities		
None	128	63
Cardiovascular disease	26	12.8
Diabetes mellitus	12	5.9
Others	37	18.2
Duration of use of biologic (months)		
12 or less	69	34.0
13 to 36	110	54.2
37 to 72	24	11.8

Sd= standard deviation

Table 2 presents the use of non-biologic medications prior to the law suit decision to pay for the use of a biologic agent. Over 20% of the patients had not used any conventional interventions - either topical, light, or systemic agents - for psoriasis prior to launching their law suit for use of biologic agents. Topical agents were used very infrequently - in only approximately 16% of patients. Phototherapy was similarly infrequently used - in 32% of the patients. Approximately 71% of the patients had used non-biologic systemic therapy before their law suit. Given that guideline adherence requires use topical and systematic therapy before beginning biologic use, only 10 patients (16.7%) met guideline requirements.

Table 2 – Treatment prior to initiating law suit for biologic use.

	adalimumab 14 (6.9)	efalizumab 43 (21.2)	etanercept 35 (17.2)	infliximab 111 (54.7)	Total 203 (100)
Therapies					
None	1 (7.1)	12 (27.9)	6 (17.1)	25 (22.5)	44 (21.7)
Only Topical	0	0	0	0	0
Only Phototherapy	0 (0.0)	5 (11.6)	3 (8.7)	7 (6.3)	15 (7.4)
Only N-BIOSYS#	10 (71.4)	2 (4.6)	12 (34.3)	36 (32.4)	60 (29.6)
Combination of Therapies prior use of Biologic n (%)					
Topical+ Phototherapy	0	0	0	0	0
Topical + N-BIOSYS#	1 (7.1)	4 (9.3)	3 (8.6)	16(14.4)	24 (11.8)
Phototherapy + N-BIOSYS#	2 ()	18 (41.8)	8 (22.8)	22 (19.8)	50 (24.6)
Topical+Phototherapy+N-BIOSYS#	0 (0.0)	2 (4.6)	3 (8.6)	5 (4.5)	10 (4.9)
Recommended use of the biological agents according guidelines (7-10) n (%)					
Topical + N-BIOSYS	1 (7.1)	6 (14.0)	6 (17.1)	21 (18.9)	34 (16.7)

acitretin, metothrexate; ciclosporine; sd – standard deviation; PSO – psoriasis
acitretin, metothrexate; ciclosporin; sd – standard deviation; N-BIOSYS – non biologic systemic agents

Table 3 presents findings in the 91 patients who were still using a biologic agent at the time of the interview. The pattern of prior use was similar to the overall group, with 19.3% of patients having used both a topical agent and systemic therapy. All patients had visited a doctor at least once a year, but 25.2% did not undergo the recommended laboratory tests (blood count, differential count, liver function) (Table 3). Thus, only 14.2% of the patients met guideline criteria for both use of prior agents and appropriate monitoring.

Of the 203 respondents 134 (66%) perceived that they experienced important improvement with use of biologic agents, although 20 patients reported a deterioration they attributed to the biologic agents. Adverse effects severe enough to discontinue medication were reported by 23 patients (11.3%).

Table 3 - Clinical follow up and outcome judgment in patient with psoriasis still taking biologic agent.

Outcomes	adalimumab 9 (9.9)	etanercept 22 (62.9)	infliximab 60 (54.0)	Total 91(100)
Annual Review				
A *consults**	9 (100)	22 (100)	60 (100)	91(100)
B *laboratorial exams***	7 (77.8)	15 (68.2)	46 (76.7)	68 (74.8)
Clinical monitoring adequate				
C *A + B*	7 (77.8)	15 (68.9)	46 (76.4)	68 (74.8)
Therapies				
None	0 (0.0)	3 (13.6)	14 (23.3)	17 (18.7)
Only Topical	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Only Phototherapy	0 (0.0)	1 (4.5)	4 (6.7)	5 (5.5)
Only N-BIOSYS#	7 (77.8)	9 (40.9)	18 (30.0)	34 (37.4)
Combination of Therapies prior use of Biologic n (%)				
Topical + Phototherapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
D *Topical + N-BIOSYS#*	1 (11.1)	3 (13.6)	8 (13.3)	12 (13.2)
Phototherapy + N-BIOSYS#	1 (11.1)	4 (18.2)	13 (21.7)	18 (19.8)
E *Topical+Phototherapy+N-BIOSYS*	0 (0.0)	2 (9.1)	3 (5.0)	5 (5.5)
F Recommended use of the biological agents according guidelines				
D + E	1 (11.1)	5 (22.7)	11 (18.3)	17 (19.3)
Adherence of guideline				
*Prior drugs and monitoring (**C + D**)*	1 (11,1)	3 (13.6)	9 (15.0)	13 (14.2)

**at least one annual medical consult; blood differential (complete blood cell count), liver function tests;*
 # use of biologic agent after treatment with topic and one systemic non biologic agent;

DISCUSSION

Main Findings

The key finding of this investigation is that very few patients obtaining payment for use of biologic agents for treatment of psoriasis had met guideline criteria for use of non-biologic therapy prior to commencing expensive and potentially toxic biologic agents (Tables 2 and 3). In particular, topical agents had seldom been used in these patients. In addition, approximately 30% had not used any non-biologic systemic agents. Further, of those still using biologic agents approximately 25% had not undergone the recommended laboratory investigations in the prior year. Thus, complete adherence to guideline recommendations for prior therapy occurred in only 16.7% of patients and complete guideline adherence including prior therapy and laboratory monitoring in only 14.2% of those still using biologic agents (Tables 2 and 3).

The patients in this sample did not have any contraindication to the use of immunosuppressive drugs (alcohol, pleural effusion, coagulopathy, uncontrolled infection, liver disease, ascites or pregnancy) (**Table 1)**. However, the prevalent comorbidities detected in these patients involve the cardiovascular system, the main contraindication to the use of biological drugs (22). Thus, the pattern of comorbidity raises further concern regarding the use of biologic agents without, in approximately 30%, the prior use of non-biologic immunosuppressant therapy.

Strengths and limitations

Strengths of this study include our ability to obtain a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis. We were able to contact and obtain consent from 203 or 218 potentially eligible patients. We obtained pharmacy records of medication use and corroborating information from patient interviews. Duplicate review of interview recordings ensured accurate information. We surveyed a number of key guidelines including both public agencies and specialty societies from a number of countries and used as criteria only recommendations included in all the guidelines.

Possible limitations in our study include the possibility that patients memory of prior medication use may not have been accurate. In particular, approximately 20% of patients reported no prior topical, phototherapy, or system therapy prior to use of biologic agents. The interviews, however, included detailed descriptions of medications, including topical agents, and patients failure to remember the use of topical agents may be implausible. We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents, and these data are therefore suspect.

Relation to evidence and recommendations

The guidelines we reviewed were consistent in their recommendation that patients with severe psoriasis who do not respond or have a contraindication to or are intolerant to topical therapy and systemic therapy with immunosuppressant, including cyclosporine and methotrexate, are candidates for biologic therapies [6-9 15]. The guidelines also recommended phototherapy as an alternative. Despite evidence of the cost-effectiveness of phototherapy in moderate-to-severe psoriasis [18 19], guidelines did not insist on a trial of phototherapy before treatment with biologic agents. .

Biologic agents may be associated with serious side effects, including an increase in the risk of malignancies opportunistic fungal infection, and lymphoma [11-13]. A particular concern is the use of drugs over the long term. Current the data available is insufficient to draw clear and reliable conclusions about either the efficacy of long-term treatments or the frequency of adverse effects over the long term [20-22]. The majority of plaintiffs are using biologics for over a year, and more than 10% for over three years, raising another possible concern.

Implications.

Biologic agents are not included in Brazilian official guideline to treat psoriasis. Therefore, access to this medication is largely from prescriptions by private practioners. Having obtained a prescription for a biologic agent, Brazilian citizen can launch legal action to have the government pay for the high cost medication. It is perhaps ironic that despite the last report of the Brazilian health assessment technology committee (Conitec) choosing to not recommend (1) the use of these biological drugs in the treatment of psoriasis primarily because of safety concerns, judicial decisions in favor of their use requires the public health system to provide funding.

Irrespective of issues of whether governments should fund biologics in psoriasis at all, clinical practice and judicial decisions should be consistent with highly credible international guidelines. Our results show an important gap between clinical practice and judicial decisions in treatments prescribed to plaintiffs demanding medicines for PSO in São Paulo, Brazil and corresponding guidelines.

Explanations for inappropriate practice include inadequate training and knowledge of the physicians who prescribe the drugs (22, 29). Another possibility is that incentives from the pharmaceutical industry are influencing the prescription of biologic agents in psoriasis. Whatever the reason, our findings demonstrate that the court system is not functioning well. Independent review by disinterested experts would have led the court to insist on appropriate prior treatment before considering biologic agents. The health system also appears negligent in not ensuring optimal follow-up to patients who receive payment for their drugs from the government. Our results suggest changes at both the level of clinical practice and the function of the judicial system are urgently needed.

What is already known on this subject?

Guidelines specify the circumstances in which biologic agents should be used in patients with psoriasis and the monitoring such patients should undergo. The extent to which clinicians follow these guidelines in a variety of clinical situations remains uncertain.

What this study adds?

In Brazil, major discrepancies exist between the management of patients who receive funding for biologic agents from the government through lawsuits and the management guidelines recommend. The majority of patients have not had the appropriate trials of less toxic drugs, and laboratory monitoring is suboptimal in approximately 25% of patients.

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✓ **TITLE: Adherence to guidelines in use of biological agents to treat psoriasis in Brazil**

ABSTRACT

[BACKGROUND]: In São Paulo, Brazil, patients gain funding for biological agents for treatment of psoriasis through lawsuits to the government. The extent to which management of such patients adhere to authoritative guidelines is uncertain.

[OBJECTIVE]: To determine the extent to which clinical practice adheres to authoritative guidelines in patients receiving treatment for psoriasis through lawsuits.

[METHODS]: We identified patients through records of the State Health Secretariat of São Paulo from 2004 to 2011. We consulted guidelines from five countries and chose as standards only those recommendations that the guidelines uniformly endorsed. Pharmacy records provided data regarding biologic use. Guidelines recommended biologics agents only in patients with severe psoriasis who have failed to respond to both topical and systemic therapies (e.g. cyclosporine and methotrexate) and recommended yearly monitoring of blood counts and liver function.

[RESULTS]: Of 218 patients identified in the database, 3 did not meet eligibility criteria and 12 declined participation. Of 203 patients interviewed, 91 were still using biological medicine; we established adherence to laboratory monitoring in these patients. In the total sample, management failed to meet standards of prior use of topical and systemic medication in 169 (83.2%) of the patients. .Of the 91 patient using biological medicine at the time of the survey, 23 (25.2%) did not undergo appropriate laboratory tests.

[CONCLUSIONS]: Important discrepancies exist between clinical practice and the recommendations of guidelines the management of plaintiffs using biologic drugs to treat psoriasis.

Strengths and limitations

1. Strengths of this study include our ability to obtain a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis.
2. We obtained pharmacy records of medication use and corroborating information from patient interviews.
3. Duplicate review of interview recordings ensured accurate information.
4. Possible limitations in our study include the possibility that patients memory of prior medication use may not have been accurate.
5. The interviews, however, included detailed descriptions of medications, including topical agents, and patients' failure to remember the use of topical agents may be implausible.
6. We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents, and these data are therefore suspect.
7. We did not study the management of patients who have received biologics through the usual health care system.

INTRODUCTION

Psoriasis, chronic inflammatory immune-mediated skin disease that predominantly affects the skin and joints occurs in between 1.5 to 3% of the population[1]. Onset may occur at any age but peaks in the second and third decades. The severity of psoriasis varies widely, and its course is characterized by relapses and remissions, though it usually persists throughout life. Its negative impact on health-related quality of life is similar to that of ischemic heart disease, diabetes, depression and cancer [2].

The significant reduction in quality of life and the psychosocial disability suffered by patients highlight the need for prompt, effective treatment, and long-term disease control[3 4]. In mild psoriasis, topical treatment can be effective[5]. Those with moderate to severe disease often require treatment with phototherapy and systemic treatment[6]. When systemic traditional treatment with cyclosporine, methotrexate, or acitretin fail (non-biologic systemic agents or N-BISYS), systemic biological therapies such as the tumor necrosis factor antagonists' adalimumab, etanercept and infliximab, and the monoclonal antibody ustekimumab that targets interleukin-12 (IL-12) and IL-23 become options.[6-9].

Due to their immunosuppressive activity, some anti-TNFs have been associated with a small increased risk of infection in patients with psoriasis[10], and studies of TNF antagonist use in other disease areas have raised concerns over a potential link to cardiovascular side-effects, malignancies, and neurological defects[10-12]. Guidelines uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents.

In Brazil patients can, once they are prescribed by a clinician, go to the courts to force the state to pay for expensive medication such as biologics. Court decisions may not be consistent with optimal standards of care in terms of patients who are appropriate for use of biologics. Furthermore, once patients receive biologics through court decisions, subsequent management may not be optimal.

The objective of this study was to identify standards of management of psoriasis common to major international guidelines and to evaluate the extent to which Brazilian physicians who prescribed biologics that courts approved on the basis of law suits adhered to these standards.

METHODS

The protocol (cross-sectional design) was authorized by the State Department of Health (SES-SP) and also approved by the ethics committee for clinical research of University of Sorocaba on August 17, 2009, with protocol number 011/2009.

Choice of Guidelines and Guideline Recommendations

We consulted guidelines from the following countries: United Kingdom[13], Germany[7], Brazil,[9] United States[14], Canada[15] and European[16]. We used both national guidelines (NICE, SIGN)[5 6] and specialty society guidelines. We reviewed all recommendations in each guideline and chose as standards only those recommendations that for prior treatment were uniformly endorsed across all guidelines and for monitoring were endorsed by 4 of the 5 guidelines.

Recommendations uniformly endorsed by every guideline[5-9]specified that biologics should only be used in patients with severe psoriasis who had failed to respond to, have a contraindication to, or are intolerant of topical therapies, and at least one systemic therapy (e.g. cyclosporine or methotrexate). Guidelines also uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents and also to evaluate control of psoriasis. Guidelines specified that the review should include monitoring of complete blood cell count and liver function tests.

Eligibility Criteria

Patients were eligible if they had, through lawsuits filed against the state of São Paulo in the period 2004-2010, gained access to biologics for treatment of psoriasis. All patients gave informed consent.

Identification of Patients and Collection of Patient Data

In order to identify eligible patients, two researchers abstracted data from all the dispensing orders in the database for psoriasis - identified by ICD code L40 - originating from lawsuits from 2004-2010 including the name, address and telephone number, gender, age, healthcare provider, whether that provider worked in the public or private system, type of biologic dispensed, and diagnoses. We excluded patient with arthritis psoriatic.

We contacted patients with psoriasis by telephone, and if they proved eligible and agreed to participate in the study, conducted interviews. The interviews were conducted by telephone using Computer Assisted Telephonic Interviews (ITAC) technology with a microcomputer handset with headphones. This system allows recording and monitoring of the duration of the conversation [17 18]. Research staff working in pairs independently recorded data from the interviews, with discrepancies resolved by the principle investigator (LL).

The interview schedule was developed in consultation with a local dermatologist (see **Appendix)** after consideration of the recommendations consistent across guidelines. An electronic form was developed in Microsoft Office Access based on the instrument developed for the interviews. To address the items listed in the instrument, 16 screens were designed to record the data from the interviews. Each interviewer received training on use of language related to each question in the interview schedule. The questionnaire included the following: what drugs the patient was using for the treatment of psoriasis prior to the court judgment, the time of diagnosis of psoriasis, comorbidities and whether patients received at least annual review. For patients still taking biologics we determined if they had received a medical consultation in the previous year and what tests had been undertaken in the previous year. In Brazil, patients receive records of all their laboratory tests and typically retain these records indefinitely; all patients still receiving biologics reported that they had retained records of all of laboratory tests undertaken during the previous year.

Patients' report of the period in which they used the biologics were cross-checked with data obtained from pharmacy records and from legal records form lawsuits. Legal records form lawsuits gave us the name of patients, name of the drugs obtained through the law suit, whether the prescription came from private or public insurance, sex, diagnostic and age of patients. If we found discrepancy between the three sources of information, we considered the information from pharmacy records definitive. Thus, definitive information about the name of the biologic and the duration of use of the biologic was obtained from the pharmacy, and definitive information of the time of diagnosis, use of previous medicines, and laboratory results was obtained from the patient. We considered guideline adherence adequate when court decisions and subsequent clinical care had adhered to all recommendations from guidelines.

In the interviews we also asked patients about their adverse effects and whether these led to discontinuing medications and their perception of the effectiveness of the biologic agents.

RESULTS

We reviewed 25,184 lawsuits that had succeeded in obtaining medicines, dietary supplements, or other health products, such as orthotics and prosthetics, and diagnostic and therapeutic procedures in the period deposited in the Public Finance Courts Capital in period 2004 to 2010. Of 218 patients identified as using biologics for psoriasis, in 3 the contact information was a law office that did not allow us to contact patients, 1 patient had died, 2 had never used the biologic that was mandated by the court decision, and 9 refused the interview. We interviewed 203 patients, of whom 91 (44.8%) were still using a biologic agent (Figure 1).

Eligible patients received one of four biologic drugs: adalimumab, etanercept, infliximab and efalizumab. Table 1 presents the socio demographic and medical health characteristics of the 203 eligible patients as well as the duration patients used the biologic agents granted payment by the courts. Over a third of the patients used the biologic agents for less than a year, and over 50% for 1 to 3 years.

Table 1 - Baseline characteristics of plaintiffs with psoriasis

	Patients N=203	%
City of residence		
São Paulo	122	60
Other	81	40
Health care		
Private	141	69.5
Sex		
Male	*129*	*63.5*
Age (years)		
19 - 59	156	76.9
≥ 60	47	23.1
mean ± sd		48.9 ± 13.7
Time of diagnosis (years previous)		
6 or more	177	84.9
2 - 5	25	10.2
≤1 year	1	0.5
Comorbidities		
None	128	63
Cardiovascular disease	26	12.8
Diabetes mellitus	12	5.9
Others	37	18.2
Duration of use of biologic (months)		
12 or less	69	34.0
13 to 36	110	54.2
37 to 72	24	11.8

Sd= standard deviation

Table 2 presents the use of non-biologic medications prior to the law suit decision to pay for the use of a biologic agent. Over 20% of the patients had not used any conventional interventions - either topical, light, or systemic agents - for psoriasis prior to launching their law suit for use of biologic agents. Topical agents were used very infrequently - in only approximately 16% of patients. Phototherapy was similarly infrequently used - in 36.9% of the patients. Approximately 71% of the patients had used non-biologic systemic therapy before their law suit. No patients had contraindications, or were using drugs with problematic interactions, that would have prevented the use of all recommended systemic agents (cyclosporine, methotrexate, and acitretin). Given that guideline adherence requires use topical and systematic therapy before beginning biologic use, only 34 patients (16.7%) met guideline requirements.

Table 2 – Treatment prior to initiating law suit for biologic use.

	adalimumab 14 (6.9)	efalizumab 43 (21.2)	etanercept 35 (17.2)	infliximab 111 (54.7)	Total 203 (100)
Therapies					
None	1 (7.1)	12 (27.9)	6 (17.1)	25 (22.5)	44 (21.7)
Only Topical	0	0	0	0	0
Only Phototherapy	0 (0.0)	5 (11.6)	3 (8.7)	7 (6.3)	15 (7.4)
Only N-BIOSYS#	10 (71.4)	2 (4.6)	12 (34.3)	36 (32.4)	60 (29.6)
Combination of Therapies prior use of Biologic n (%)					
Topical+ Phototherapy	0	0	0	0	0
Topical + N-BIOSYS#	1 (7.1)	4 (9.3)	3 (8.6)	16(14.4)	24 (11.8)
Phototherapy + N-BIOSYS#	2 ()	18 (41.8)	8 (22.8)	22 (19.8)	50 (24.6)
Topical+Phototherapy+N-BIOSYS#	0 (0.0)	2 (4.6)	3 (8.6)	5 (4.5)	10 (4.9)
Recommended use of the biological agents according guidelines (7-10) n (%)					
Topical + N-BIOSYS	1 (7.1)	6 (14.0)	6 (17.1)	21 (18.9)	34 (16.7)

acitretin, metothrexate; ciclosporine; sd – standard deviation; PSO – psoriasis
acitretin, metothrexate; ciclosporin; sd – standard deviation; N-BIOSYS – non biologic systemic agents

Table 3 presents findings in the 91 patients who were still using a biologic agent at the time of the interview. The pattern of prior use was similar to the overall group, with 19.3% of patients having used both a topical agent and systemic therapy. All patients had visited a doctor at least once a year, but 25.2% did not undergo the recommended laboratory tests (blood count, differential count, liver function) (Table 3). Thus, only 14.2% of the patients met guideline criteria for both use of prior agents and appropriate monitoring.

Of the 203 respondents 134 (66%) perceived that they experienced important improvement with use of biologic agents, although 20 patients reported a deterioration they attributed to the biologic agents. Adverse effects severe enough to discontinue medication were reported by 23 patients (11.3%).

Table 3 - Clinical follow up and outcome judgment in patient with psoriasis still taking biologic agent.

Outcomes	adalimumab 9 (9.9)	etanercept 22 (62.9)	infliximab 60 (54.0)	Total 91(100)
Annual Review				
A *consults**	9 (100)	22 (100)	60 (100)	91(100)
B *laboratorial exams***	7 (77.8)	15 (68.2)	46 (76.7)	68 (74.8)
Clinical monitoring adequate				
C *A + B*	7 (77.8)	15 (68.9)	46 (76.4)	68 (74.8)
Therapies				
None	0 (0.0)	3 (13.6)	14 (23.3)	17 (18.7)
Only Topical	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Only Phototherapy	0 (0.0)	1 (4.5)	4 (6.7)	5 (5.5)
Only N-BIOSYS#	7 (77.8)	9 (40.9)	18 (30.0)	34 (37.4)
Combination of Therapies prior use of Biologic n (%)				
Topical + Phototherapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
D *Topical + N-BIOSYS#*	1 (11.1)	3 (13.6)	8 (13.3)	12 (13.2)
Phototherapy + N-BIOSYS#	1 (11.1)	4 (18.2)	13 (21.7)	18 (19.8)
E *Topical+Phototherapy+N-BIOSYS*	0 (0.0)	2 (9.1)	3 (5.0)	5 (5.5)
F Recommended use of the biological agents according guidelines				
D + E	1 (11.1)	5 (22.7)	11 (18.3)	17 (19.3)
Adherence of guideline				
*Prior drugs and monitoring (**C + D**)*	1 (11,1)	3 (13.6)	9 (15.0)	13 (14.2)

**at least one annual medical consult; blood differential (complete blood cell count), liver function tests;*

 # use of biologic agent after treatment with topic and one systemic non biologic agent;

DISCUSSION

Main Findings

The key finding of this investigation is that very few patients obtaining payment for use of biologic agents for treatment of psoriasis had met guideline criteria for use of non-biologic therapy prior to commencing expensive and potentially toxic biologic agents (Tables 2 and 3). In particular, topical agents had seldom been used in these patients. In addition, approximately 30% had not used any non-biologic systemic agents. Further, of those still using biologic agents approximately 25% had not undergone the recommended laboratory investigations in the prior year. Thus, complete adherence to guideline recommendations for

prior therapy occurred in only 16.7% of patients and complete guideline adherence including prior therapy and laboratory monitoring in only 14.2% of those still using biologic agents (Tables 2 and 3).

The patients in this sample did not have heart failure, the only universally agreed upon contraindication to the use of immunosuppressive drugs (**Table 1)**. However, the prevalent comorbidities detected in these patients involve the cardiovascular system, the main contraindication to the use of biological drugs (22). Thus, the pattern of comorbidity raises further concern regarding the use of biologic agents without, in approximately 30%, the prior use of non-biologic immunosuppressant therapy.

Strengths and weaknesses of the study

Strengths of this study include our ability to obtain a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis. We were able to contact and obtain consent from 203 or 218 potentially eligible patients. We obtained pharmacy records of medication use and corroborating information from patient interviews. Duplicate review of interview recordings ensured accurate information. We surveyed a number of key guidelines including both public agencies and specialty societies from a number of countries and used as criteria only recommendations included in all the guidelines.

Possible limitations in our study include the possibility that patient's memory of prior medication use may not have been accurate. In particular, approximately 20% of patients reported no prior topical, phototherapy, or system therapy prior to use of biologic agents. The interviews, however, included detailed descriptions of medications, including topical agents, and patients' failure to remember the use of topical agents may be implausible. We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents, and these data are therefore suspect.

Also we did not study the management of patients who have received biologics through the usual health care system (i.e. without recourse to the courts) represents another limitation of the study Thus, our study provides only indirect evidence regarding how these patients are managed within the Brazilian system".

Relation to evidence and recommendations

The guidelines we reviewed were consistent in their recommendation that patients with severe psoriasis who do not respond or have a contraindication to or are intolerant to topical therapy and systemic therapy with immunosuppressant, including cyclosporine and methotrexate, are candidates for biologic therapies [5-8 15]. The guidelines also recommended phototherapy as an alternative. Despite evidence of the cost-effectiveness of phototherapy in moderate-to-severe psoriasis [19 20], guidelines did not insist on a trial of phototherapy before treatment with biologic agents. .

Biologic agents may be associated with serious adverse effects, including an increase in the risk of malignancies opportunistic fungal infection, and lymphoma [10-12]. A particular concern is the use of drugs over the long term. Current the data available is insufficient to draw clear and reliable conclusions about either the efficacy of long-term treatments or the frequency of adverse effects over the long term [21-23]. The majority of plaintiffs are using biologics for over a year, and more than 10% for over three years, raising another possible concern.

Implications.

Biologic agents are not included in Brazilian official guideline to treat psoriasis. Therefore, access to this medication is largely from prescriptions by private practioners. Having obtained a prescription for a biologic agent, Brazilian citizen can launch legal action to have the government pay for the high cost medication. It is perhaps ironic that despite the last report of the Brazilian health assessment technology committee (Conitec) choosing to not recommend (1) the use of these biological drugs in the treatment of psoriasis primarily because of safety concerns, judicial decisions in favor of their use requires the public health system to provide funding.

One could argue that it may be unreasonable to ask judges to be aware of medical guidelines, particularly those arising from other jurisdictions. A proposed solution to this problem would be to provide the court with high quality technical analyses. In this case, experts in psoriasis aware of the guidelines would provide the analyses. So far, such analyses are unavailable [24-26]. Our results emphasize the need for technical analyses to guide court decisions, ideally considering two independent opinions.

Irrespective of issues of whether governments should fund biologics in psoriasis at all, clinical practice and judicial decisions should be consistent with highly credible international guidelines. Our results show an important gap between clinical practice and judicial

decisions in treatments prescribed to plaintiffs demanding medicines for Psoriasis in São Paulo, Brazil and corresponding guidelines.

Explanations for inappropriate practice include inadequate training and knowledge of the physicians who prescribe the drugs[27 28]. Another possibility is that incentives from the pharmaceutical industry are influencing the prescription of biologic agents in psoriasis. Whatever the reason, our findings demonstrate that the court system is not functioning well. This is not necessarily the fault of the judges, but of a system that does not ensure that judges have the appropriate access to expert guidance. Independent review by disinterested experts would have led the court to insist on appropriate prior treatment before considering biologic agents. The health system also appears negligent in not ensuring optimal follow-up to patients who receive payment for their drugs from the government. The responsibility for informing practitioners of optimal management could rest with the pharmaceutical industry, the national dermatologic society, or the government.

Our results suggest changes at both the level of clinical practice and the function of the judicial system are urgently needed.

What is already known on this subject?

Guidelines specify the circumstances in which biologic agents should be used in patients with psoriasis and the monitoring such patients should undergo. The extent to which clinicians follow these guidelines in a variety of clinical situations remains uncertain.

What this study adds?

In Brazil, major discrepancies exist between the management of patients who receive funding for biologic agents from the government through lawsuits and the management guidelines recommend. The majority of patients have not had the appropriate trials of less toxic drugs, and laboratory monitoring is suboptimal in approximately 25% of patients.

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Contributors: LL, IC, SBF and COC had the original idea and they developed the study protocol. GG, LL, MS and COC performed data analysis and drafted the manuscript. MS, FSDF, SBF, MCC and IC contributed to data collection. All authors contributed to the preparation of the manuscript and read and approved the final version.

Competing interests: none.

Ethics approval: this study is part of PSAR Project approved by committee for clinical research of University of Sorocaba on August 17, 2009, with protocol number 011/2009.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	FIGURE 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	TABLE 1, PAGE 8
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9, 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	9, 10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

TITLE: Adherence to guidelines in use of biological agents to treat psoriasis in Brazil

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[BACKGROUND]: In São Paulo, Brazil, patients gain funding for biological agents for treatment of psoriasis through lawsuits to the government. The extent to which management of such patients adhere to authoritative guidelines is uncertain.

[OBJECTIVE]: To determine the extent to which clinical practice adheres to authoritative guidelines in patients receiving treatment for psoriasis through lawsuits.

[METHODS]: We identified patients through records of the State Health Secretariat of São Paulo from 2004 to 2011. We consulted guidelines from five countries and chose as standards only those recommendations that the guidelines uniformly endorsed. Pharmacy records provided data regarding biologic use. Guidelines recommended biologics agents only in patients with severe psoriasis who have failed to respond to both topical and systemic therapies (e.g. cyclosporine and methotrexate) and recommended yearly monitoring of blood counts and liver function.

[RESULTS]: Of 218 patients identified in the database, 3 did not meet eligibility criteria and 12 declined participation. Of 203 patients interviewed, 91 were still using biological medicine; we established adherence to laboratory monitoring in these patients. In the total sample, management failed to meet standards of prior use of topical and systemic medication in 169 (83.2%) of the patients. .Of the 91 patient using biological medicine at the time of the survey, 23 (25.2%) did not undergo appropriate laboratory tests.

[CONCLUSIONS]: Important discrepancies exist between clinical practice and the recommendations of guidelines the management of plaintiffs using biologic drugs to treat psoriasis.

Strengths and limitations

1. Strengths of this study include our ability to obtain a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis.
2. We obtained pharmacy records of medication use and corroborating information from patient interviews.
3. Duplicate review of interview recordings ensured accurate information.
4. Possible limitations in our study include the possibility that patients memory of prior medication use may not have been accurate.
5. The interviews, however, included detailed descriptions of medications, including topical agents, and patients' failure to remember the use of topical agents may be implausible.
6. We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents, and these data are therefore suspect.
7. *We did not study the management of patients who have received biologics through the usual health care system*

INTRODUCTION

Psoriasis, chronic inflammatory immune-mediated skin disease that predominantly affects the skin and joints occurs in between 1.5 to 3% of the population[1]. Onset may occur at any age but peaks in the second and third decades. The severity of psoriasis varies widely, and its course is characterized by relapses and remissions, though it usually persists throughout life. Its negative impact on health-related quality of life is similar to that of ischemic heart disease, diabetes, depression and cancer [2].

The significant reduction in quality of life and the psychosocial disability suffered by patients highlight the need for prompt, effective treatment, and long-term disease control[3 4]. In mild psoriasis, topical treatment can be effective[5]. Those with moderate to severe disease often require treatment with phototherapy and systemic treatment[6]. When systemic traditional treatment with cyclosporine, methotrexate, or acitretin fail (non-biologic systemic agents or N-BISYS), systemic biological therapies such as the tumor necrosis factor antagonists' adalimumab, etanercept and infliximab, and the monoclonal antibody ustekimumab that targets interleukin-12 (IL-12) and IL-23 become options.[6-9].

Due to their immunosuppressive activity, some anti-TNFs have been associated with a small increased risk of infection in patients with psoriasis[10], and studies of TNF antagonist use in other disease areas have raised concerns over a potential link to cardiovascular side-effects, malignancies, and neurological defects[10-12]. Guidelines uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents.

In Brazil patients can, once they are prescribed by a clinician, go to the courts to force the state to pay for expensive medication such as biologics. Court decisions may not be consistent with optimal standards of care in terms of patients who are appropriate for use of biologics. Furthermore, once patients receive biologics through court decisions, subsequent management may not be optimal.

The objective of this study was to identify standards of management of psoriasis common to major international guidelines and to evaluate the extent to which Brazilian physicians who prescribed biologics that courts approved on the basis of law suits adhered to these standards.

METHODS

The protocol was authorized by the State Department of Health (SES-SP) and also approved by the ethics committee for clinical research of University of Sorocaba on August 17, 2009, with protocol number 011/2009.

Choice of Guidelines and Guideline Recommendations

We consulted guidelines from the following countries: United Kingdom[13], Germany[7], Brazil,[9] United States[14], Canada[15] and European[16]. We used both national guidelines (NICE, SIGN)[5 6] and specialty society guidelines. We reviewed all recommendations in each guideline and chose as standards only those recommendations that for prior treatment were uniformly endorsed across all guidelines and for monitoring were endorsed by 4 of the 5 guidelines.

Recommendations uniformly endorsed by every guideline[5-9]specified that biologics should only be used in patients with severe psoriasis who had failed to respond to, have a contraindication to, or are intolerant of topical therapies, and at least one systemic therapy (e.g. cyclosporine or methotrexate). Guidelines also uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents and also to evaluate control of psoriasis. Guidelines specified that the review should include monitoring of complete blood cell count and liver function tests.

Eligibility Criteria

Patients were eligible if they had, through lawsuits filed against the state of São Paulo in the period 2004-2010, gained access to biologics for treatment of psoriasis. All patients gave informed consent.

Identification of Patients and Collection of Patient Data

In order to identify eligible patients, two researchers abstracted data from all the dispensing orders in the database for psoriasis - identified by ICD code L40 - originating from lawsuits from 2004-2010 including the name, address and telephone number, gender, age, healthcare provider, whether that provider worked in the public or private system, type of biologic dispensed, and diagnoses. We excluded patient with arthritis psoriatic.

We contacted patients with psoriasis by telephone, and if they proved eligible and agreed to participate in the study, conducted interviews. The interviews were conducted by telephone using Computer Assisted Telephonic Interviews (ITAC) technology with a microcomputer handset with headphones. This system allows recording and monitoring of the duration of the conversation [17 18]. Research staff working in pairs independently recorded data from the interviews, with discrepancies resolved by the principle investigator (LL).

The interview schedule was developed in consultation with a local dermatologist (see **Appendix)** after consideration of the recommendations consistent across guidelines. An electronic form was developed in Microsoft Office Access based on the instrument developed for the interviews. To address the items listed in the instrument, 16 screens were designed to record the data from the interviews. Each interviewer received training on use of language related to each question in the interview schedule. The questionnaire included the following: what drugs the patient was using for the treatment of psoriasis prior to the court judgment, the time of diagnosis of psoriasis, comorbidities and whether patients received at least annual review. For patients still taking biologics we determined if they had received a medical consultation in the previous year and what tests had been undertaken in the previous year. In Brazil, patients receive records of all their laboratory tests and typically retain these records indefinitely; all patients still receiving biologics reported that they had retained records of all of laboratory tests undertaken during the previous year.

Patients' report of the period in which they used the biologics were cross-checked with data obtained from pharmacy records and from legal records form lawsuits. Legal records form lawsuits gave us the name of patients, name of the drugs obtained through the law suit, whether the prescription came from private or public insurance, sex, diagnostic and age of patients. If we found discrepancy between the three sources of information, we considered the information from pharmacy records definitive. Thus, definitive information about the name of the biologic and the duration of use of the biologic was obtained from the pharmacy, and definitive information of the time of diagnosis, use of previous medicines, and laboratory results was obtained from the patient. We considered guideline adherence adequate when court decisions and subsequent clinical care had adhered to all recommendations from guidelines.

In the interviews we also asked patients about their adverse effects and whether these led to discontinuing medications and their perception of the effectiveness of the biologic agents.

RESULTS

We reviewed 25,184 lawsuits that had succeeded in obtaining medicines, dietary supplements, or other health products, such as orthotics and prosthetics, and diagnostic and therapeutic procedures in the period deposited in the Public Finance Courts Capital in period 2004 to 2010. Of 218 patients identified as using biologics for psoriasis, in 3 the contact information was a law office that did not allow us to contact patients, 1 patient had died, 2 had never used the biologic that was mandated by the court decision, and 9 refused the interview. We interviewed 203 patients, of whom 91 (44.8%) were still using a biologic agent (Figure 1).

Eligible patients received one of four biologic drugs: adalimumab, etanercept, infliximab and efalizumab. Table 1 presents the socio demographic and medical health characteristics of the 203 eligible patients as well as the duration patients used the biologic agents granted payment by the courts. Over a third of the patients used the biologic agents for less than a year, and over 50% for 1 to 3 years.

Table 1 - Baseline characteristics of plaintiffs with psoriasis

	Patients N=203	%
City of residence		
São Paulo	122	60
Other	81	40
Health care		
Private	141	69.5
Sex		
Male	*129*	*63.5*
Age (years)		
19 - 59	156	76.9
≥ 60	47	23.1
mean ± sd		48.9 ± 13.7
Time of diagnosis (years previous)		
6 or more	177	84.9
2 - 5	25	10.2
≤1 year	1	0.5
Comorbidities		
None	128	63
Cardiovascular disease	26	12.8
Diabetes mellitus	12	5.9
Others	37	18.2
Duration of use of biologic (months)		
12 or less	69	34.0
13 to 36	110	54.2
37 to 72	24	11.8

Sd= standard deviation

Table 2 presents the use of non-biologic medications prior to the law suit decision to pay for the use of a biologic agent. Over 20% of the patients had not used any conventional interventions - either topical, light, or systemic agents - for psoriasis prior to launching their law suit for use of biologic agents. Topical agents were used very infrequently - in only approximately 16% of patients. Phototherapy was similarly infrequently used - in 36.9% of the patients. Approximately 71% of the patients had used non-biologic systemic therapy before their law suit. No patients had contraindications, or were using drugs with problematic interactions, that would have prevented the use of all recommended systemic agents (cyclosporine, methotrexate, and acitretin). Given that guideline adherence requires use topical and systematic therapy before beginning biologic use, only 34 patients (16.7%) met guideline requirements.

Table 2 – Treatment prior to initiating law suit for biologic use.

	adalimumab 14 (6.9)	efalizumab 43 (21.2)	etanercept 35 (17.2)	infliximab 111 (54.7)	Total 203 (100)
Therapies					
None	1 (7.1)	12 (27.9)	6 (17.1)	25 (22.5)	44 (21.7)
Only Topical	0	0	0	0	0
Only Phototherapy	0 (0.0)	5 (11.6)	3 (8.7)	7 (6.3)	15 (7.4)
Only N-BIOSYS#	10 (71.4)	2 (4.6)	12 (34.3)	36 (32.4)	60 (29.6)
Combination of Therapies prior use of Biologic n (%)					
Topical+ Phototherapy	0	0	0	0	0
Topical + N-BIOSYS#	1 (7.1)	4 (9.3)	3 (8.6)	16(14.4)	24 (11.8)
Phototherapy + N-BIOSYS#	2 ()	18 (41.8)	8 (22.8)	22 (19.8)	50 (24.6)
Topical+Phototherapy+N-BIOSYS#	0 (0.0)	2 (4.6)	3 (8.6)	5 (4.5)	10 (4.9)
Recommended use of the biological agents according guidelines (7-10) n (%)					
Topical + N-BIOSYS	1 (7.1)	6 (14.0)	6 (17.1)	21 (18.9)	34 (16.7)

acitretin, metothrexate; ciclosporine; sd – standard deviation; PSO – psoriasis
acitretin, metothrexate; ciclosporin; sd – standard deviation; N-BIOSYS – non biologic systemic agents

Table 3 presents findings in the 91 patients who were still using a biologic agent at the time of the interview. The pattern of prior use was similar to the overall group, with 19.3% of patients having used both a topical agent and systemic therapy. All patients had visited a doctor at least once a year, but 25.2% did not undergo the recommended laboratory tests (blood count, differential count, liver function) (Table 3). Thus, only 14.2% of the patients met guideline criteria for both use of prior agents and appropriate monitoring.

Of the 203 respondents 134 (66%) perceived that they experienced important improvement with use of biologic agents, although 20 patients reported a deterioration they attributed to the biologic agents. Adverse effects severe enough to discontinue medication were reported by 23 patients (11.3%).

Table 3 - Clinical follow up and outcome judgment in patient with psoriasis still taking biologic agent.

Outcomes	adalimumab 9 (9.9)	etanercept 22 (62.9)	infliximab 60 (54.0)	Total 91(100)
Annual Review				
A *consults**	9 (100)	22 (100)	60 (100)	91(100)
B *laboratorial exams***	7 (77.8)	15 (68.2)	46 (76.7)	68 (74.8)
Clinical monitoring adequate				
C *A + B*	7 (77.8)	15 (68.9)	46 (76.4)	68 (74.8)
Therapies				
None	0 (0.0)	3 (13.6)	14 (23.3)	17 (18.7)
Only Topical	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Only Phototherapy	0 (0.0)	1 (4.5)	4 (6.7)	5 (5.5)
Only N-BIOSYS#	7 (77.8)	9 (40.9)	18 (30.0)	34 (37.4)
Combination of Therapies prior use of Biologic n (%)				
Topical + Phototherapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
D *Topical + N-BIOSYS#*	1 (11.1)	3 (13.6)	8 (13.3)	12 (13.2)
Phototherapy + N-BIOSYS#	1 (11.1)	4 (18.2)	13 (21.7)	18 (19.8)
E *Topical+Phototherapy+N-BIOSYS*	0 (0.0)	2 (9.1)	3 (5.0)	5 (5.5)
F Recommended use of the biological agents according guidelines				
D + E	1 (11.1)	5 (22.7)	11 (18.3)	17 (19.3)
Adherence of guideline				
*Prior drugs and monitoring (**C + D**)*	1 (11,1)	3 (13.6)	9 (15.0)	13 (14.2)

**at least one annual medical consult; blood differential (complete blood cell count), liver function tests;*
 # use of biologic agent after treatment with topic and one systemic non biologic agent;

DISCUSSION

Main Findings

The key finding of this investigation is that very few patients obtaining payment for use of biologic agents for treatment of psoriasis had met guideline criteria for use of non-biologic therapy prior to commencing expensive and potentially toxic biologic agents (**Tables 2 and 3).** In particular, topical agents had seldom been used in these patients. In addition, approximately 30% had not used any non-biologic systemic agents. Further, of those still using biologic agents approximately 25% had not undergone the recommended laboratory investigations in the prior year. Thus, complete adherence to guideline recommendations for prior therapy occurred in only 16.7% of patients and complete guideline adherence including prior therapy and laboratory monitoring in only 14.2% of those still using biologic agents (Tables 2 and 3).

The patients in this sample did not have heart failure, the only universally agreed upon ~~any~~ contraindication to the use of immunosuppressive drugs ~~(alcohol, pleural effusion, coagulopathy, uncontrolled infection, liver disease, ascites or pregnancy)~~ (**Table 1**). However, the prevalent comorbidities detected in these patients involve the cardiovascular system, the main contraindication to the use of biological drugs (22). Thus, the pattern of comorbidity raises further concern regarding the use of biologic agents without, in approximately 30%, the prior use of non-biologic immunosuppressant therapy.

Strengths and weaknesses of the study

Strengths of this study include our ability to obtain a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis. We were able to contact and obtain consent from 203 or 218 potentially eligible patients. We obtained pharmacy records of medication use and corroborating information from patient interviews. Duplicate review of interview recordings ensured accurate information. We surveyed a number of key guidelines including both public agencies and specialty societies from a number of countries and used as criteria only recommendations included in all the guidelines.

Possible limitations in our study include the possibility that patient's memory of prior medication use may not have been accurate. In particular, approximately 20% of patients reported no prior topical, phototherapy, or system therapy prior to use of biologic agents. The interviews, however, included detailed descriptions of medications, including topical agents, and patients' failure to remember the use of topical agents may be implausible. We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents, and these data are therefore suspect.

Also we did not study the management of patients who have received biologics through the usual health care system (i.e. without recourse to the courts) represents another limitation of the study Thus, our study provides only indirect evidence regarding how these patients are managed within the Brazilian system".

Relation to evidence and recommendations

The guidelines we reviewed were consistent in their recommendation that patients with severe psoriasis who do not respond or have a contraindication to or are intolerant to topical therapy and systemic therapy with immunosuppressant, including cyclosporine and

methotrexate, are candidates for biologic therapies [5-8 15]. The guidelines also recommended phototherapy as an alternative. Despite evidence of the cost-effectiveness of phototherapy in moderate-to-severe psoriasis [19 20], guidelines did not insist on a trial of phototherapy before treatment with biologic agents. .

Biologic agents may be associated with serious adverse effects, including an increase in the risk of malignancies opportunistic fungal infection, and lymphoma [10-12]. A particular concern is the use of drugs over the long term. Current the data available is insufficient to draw clear and reliable conclusions about either the efficacy of long-term treatments or the frequency of adverse effects over the long term [21-23]. The majority of plaintiffs are using biologics for over a year, and more than 10% for over three years, raising another possible concern.

Implications.

Biologic agents are not included in Brazilian official guideline to treat psoriasis. Therefore, access to this medication is largely from prescriptions by private practioners. Having obtained a prescription for a biologic agent, Brazilian citizen can launch legal action to have the government pay for the high cost medication. It is perhaps ironic that despite the last report of the Brazilian health assessment technology committee (Conitec) choosing to not recommend (1) the use of these biological drugs in the treatment of psoriasis primarily because of safety concerns, judicial decisions in favor of their use requires the public health system to provide funding.

One could argue that it may be unreasonable to ask judges to be aware of medical guidelines, particularly those arising from other jurisdictions. A proposed solution to this problem would be to provide the court with high quality technical analyses. In this case, experts in psoriasis aware of the guidelines would provide the analyses. So far, such analyses are unavailable [24-26]. Our results emphasize the need for technical analyses to guide court decisions, ideally considering two independent opinions.

Irrespective of issues of whether governments should fund biologics in psoriasis at all, clinical practice and judicial decisions should be consistent with highly credible international guidelines. Our results show an important gap between clinical practice and judicial decisions in treatments prescribed to plaintiffs demanding medicines for Psoriasis in São Paulo, Brazil and corresponding guidelines.

Explanations for inappropriate practice include inadequate training and knowledge of the physicians who prescribe the drugs[27 28]. Another possibility is that incentives from the pharmaceutical industry are influencing the prescription of biologic agents in psoriasis. Whatever the reason, our findings demonstrate that the court system is not functioning well. This is not necessarily the fault of the judges, but of a system that does not ensure that judges have the appropriate access to expert guidance. Independent review by disinterested experts would have led the court to insist on appropriate prior treatment before considering biologic agents. The health system also appears negligent in not ensuring optimal follow-up to patients who receive payment for their drugs from the government. The responsibility for informing practitioners of optimal management could rest with the pharmaceutical industry, the national dermatologic society, or the government.

Our results suggest changes at both the level of clinical practice and the function of the judicial system are urgently needed.

What is already known on this subject?

Guidelines specify the circumstances in which biologic agents should be used in patients with psoriasis and the monitoring such patients should undergo. The extent to which clinicians follow these guidelines in a variety of clinical situations remains uncertain.

What this study adds?

In Brazil, major discrepancies exist between the management of patients who receive funding for biologic agents from the government through lawsuits and the management guidelines recommend. The majority of patients have not had the appropriate trials of less toxic drugs, and laboratory monitoring is suboptimal in approximately 25% of patients.

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TITLE: Adherence to guidelines in use of biological agents to treat psoriasis in Brazil

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ABSTRACT

[BACKGROUND]: In São Paulo, Brazil, patients gain funding for biological agents for treatment of psoriasis through lawsuits to the government. The extent to which management of such patients adhere to authoritative guidelines is uncertain.

[OBJECTIVE]: To determine the extent to which clinical practice adheres to authoritative guidelines in patients receiving treatment for psoriasis through lawsuits.

[METHODS]: We identified patients through records of the State Health Secretariat of São Paulo from 2004 to 2011. We consulted guidelines from five countries and chose as standards only those recommendations that the guidelines uniformly endorsed. Pharmacy records provided data regarding biologic use. Guidelines recommended biologics agents only in patients with severe psoriasis who have failed to respond to both topical and systemic therapies (e.g. cyclosporine and methotrexate) and recommended yearly monitoring of blood counts and liver function.

[RESULTS]: Of 218 patients identified in the database, 3 did not meet eligibility criteria and 12 declined participation. Of 203 patients interviewed, 91 were still using biological medicine; we established adherence to laboratory monitoring in these patients. In the total sample, management failed to meet standards of prior use of topical and systemic medication in 169 (83.2%) of the patients. .Of the 91 patient using biological medicine at the time of the survey, 23 (25.2%) did not undergo appropriate laboratory tests.

[CONCLUSIONS]: Important discrepancies exist between clinical practice and the recommendations of guidelines the management of plaintiffs using biologic drugs to treat psoriasis.

Strengths and limitations

1. Strengths of this study include our ability to obtain a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis.
2. We obtained pharmacy records of medication use and corroborating information from patient interviews.
3. Duplicate review of interview recordings ensured accurate information.
4. Possible limitations in our study include the possibility that patients memory of prior medication use may not have been accurate.
5. The interviews, however, included detailed descriptions of medications, including topical agents, and patients' failure to remember the use of topical agents may be implausible.
6. We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents, and these data are therefore suspect.
7. We did not study the management of patients who have received biologics through the usual health care system.

INTRODUCTION

Psoriasis, chronic inflammatory immune-mediated skin disease that predominantly affects the skin and joints occurs in between 1.5 to 3% of the population[1]. Onset may occur at any age but peaks in the second and third decades. The severity of psoriasis varies widely, and its course is characterized by relapses and remissions, though it usually persists throughout life. Its negative impact on health-related quality of life is similar to that of ischemic heart disease, diabetes, depression and cancer [2].

The significant reduction in quality of life and the psychosocial disability suffered by patients highlight the need for prompt, effective treatment, and long-term disease control[3 4]. In mild psoriasis, topical treatment can be effective[5]. Those with moderate to severe disease often require treatment with phototherapy and systemic treatment[6]. When systemic traditional treatment with cyclosporine, methotrexate, or acitretin fail (non-biologic systemic agents or N-BISYS), systemic biological therapies such as the tumor necrosis factor antagonists' adalimumab, etanercept and infliximab, and the monoclonal antibody ustekimumab that targets interleukin-12 (IL-12) and IL-23 become options.[6-9].

Due to their immunosuppressive activity, some anti-TNFs have been associated with a small increased risk of infection in patients with psoriasis[10], and studies of TNF antagonist use in other disease areas have raised concerns over a potential link to cardiovascular side-effects, malignancies, and neurological defects[10-12]. Guidelines uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents.

In Brazil patients can, once they are prescribed by a clinician, go to the courts to force the state to pay for expensive medication such as biologics. Court decisions may not be consistent with optimal standards of care in terms of patients who are appropriate for use of biologics. Furthermore, once patients receive biologics through court decisions, subsequent management may not be optimal.

The objective of this study was to identify standards of management of psoriasis common to major international guidelines and to evaluate the extent to which Brazilian physicians who prescribed biologics that courts approved on the basis of law suits adhered to these standards.

METHODS

The protocol (cross-sectional design) was authorized by the State Department of Health (SES-SP) and also approved by the ethics committee for clinical research of University of Sorocaba on August 17, 2009, with protocol number 011/2009.

Choice of Guidelines and Guideline Recommendations

We consulted guidelines from the following countries: United Kingdom[13], Germany[7], Brazil,[9] United States[14], Canada[15] and European[16]. We used both national guidelines (NICE, SIGN)[5 6] and specialty society guidelines. We reviewed all recommendations in each guideline and chose as standards only those recommendations that for prior treatment were uniformly endorsed across all guidelines and for monitoring were endorsed by 4 of the 5 guidelines.

Recommendations uniformly endorsed by every guideline[5-9]specified that biologics should only be used in patients with severe psoriasis who had failed to respond to, have a contraindication to, or are intolerant of topical therapies, and at least one systemic therapy (e.g. cyclosporine or methotrexate). Guidelines also uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents and also to evaluate control of psoriasis. Guidelines specified that the review should include monitoring of complete blood cell count and liver function tests.

Eligibility Criteria

Patients were eligible if they had, through lawsuits filed against the state of São Paulo in the period 2004-2010, gained access to biologics for treatment of psoriasis. All patients gave informed consent.

Identification of Patients and Collection of Patient Data

In order to identify eligible patients, two researchers abstracted data from all the dispensing orders in the database for psoriasis - identified by ICD code L40 - originating from lawsuits from 2004-2010 including the name, address and telephone number, gender, age, healthcare provider, whether that provider worked in the public or private system, type of biologic dispensed, and diagnoses. We excluded patient with arthritis psoriatic.

We contacted patients with psoriasis by telephone, and if they proved eligible and agreed to participate in the study, conducted interviews. The interviews were conducted by telephone using Computer Assisted Telephonic Interviews (ITAC) technology with a microcomputer handset with headphones. This system allows recording and monitoring of the duration of the conversation [17 18]. Research staff working in pairs independently recorded data from the interviews, with discrepancies resolved by the principle investigator (LL).

The interview schedule was developed in consultation with a local dermatologist (see **Appendix)** after consideration of the recommendations consistent across guidelines. An electronic form was developed in Microsoft Office Access based on the instrument developed for the interviews. To address the items listed in the instrument, 16 screens were designed to record the data from the interviews. Each interviewer received training on use of language related to each question in the interview schedule. The questionnaire included the following: what drugs the patient was using for the treatment of psoriasis prior to the court judgment, the time of diagnosis of psoriasis, comorbidities and whether patients received at least annual review. For patients still taking biologics we determined if they had received a medical consultation in the previous year and what tests had been undertaken in the previous year. In Brazil, patients receive records of all their laboratory tests and typically retain these records indefinitely; all patients still receiving biologics reported that they had retained records of all of laboratory tests undertaken during the previous year.

Patients' report of the period in which they used the biologics were cross-checked with data obtained from pharmacy records and from legal records form lawsuits. Legal records form lawsuits gave us the name of patients, name of the drugs obtained through the law suit, whether the prescription came from private or public insurance, sex, diagnostic and age of patients. If we found discrepancy between the three sources of information, we considered the information from pharmacy records definitive. Thus, definitive information about the name of the biologic and the duration of use of the biologic was obtained from the pharmacy, and definitive information of the time of diagnosis, use of previous medicines, and laboratory results was obtained from the patient. We considered guideline adherence adequate when court decisions and subsequent clinical care had adhered to all recommendations from guidelines.

In the interviews we also asked patients about their adverse effects and whether these led to discontinuing medications and their perception of the effectiveness of the biologic agents.

RESULTS

We reviewed 25,184 lawsuits that had succeeded in obtaining medicines, dietary supplements, or other health products, such as orthotics and prosthetics, and diagnostic and therapeutic procedures in the period deposited in the Public Finance Courts Capital in period 2004 to 2010. Of 218 patients identified as using biologics for psoriasis, in 3 the contact information was a law office that did not allow us to contact patients, 1 patient had died, 2 had never used the biologic that was mandated by the court decision, and 9 refused the interview. We interviewed 203 patients, of whom 91 (44.8%) were still using a biologic agent (Figure 1).

Eligible patients received one of four biologic drugs: adalimumab, etanercept, infliximab and efalizumab. Table 1 presents the socio demographic and medical health characteristics of the 203 eligible patients as well as the duration patients used the biologic agents granted payment by the courts. Over a third of the patients used the biologic agents for less than a year, and over 50% for 1 to 3 years.

Table 1 - Baseline characteristics of plaintiffs with psoriasis

	Patients N=203	%
City of residence		
São Paulo	122	60
Other	81	40
Health care		
Private	141	69.5
Sex		
Male	*129*	*63.5*
Age (years)		
19 - 59	156	76.9
≥ 60	47	23.1
mean ± sd		48.9 ± 13.7
Time of diagnosis (years previous)		
6 or more	177	84.9
2 - 5	25	10.2
≤1 year	1	0.5
Comorbidities		
None	128	63
Cardiovascular disease	26	12.8
Diabetes mellitus	12	5.9
Others	37	18.2
Duration of use of biologic (months)		
12 or less	69	34.0
13 to 36	110	54.2
37 to 72	24	11.8

Sd= standard deviation

Table 2 presents the use of non-biologic medications prior to the law suit decision to pay for the use of a biologic agent. Over 20% of the patients had not used any conventional interventions - either topical, light, or systemic agents - for psoriasis prior to launching their law suit for use of biologic agents. Topical agents were used very infrequently - in only approximately 16% of patients. Phototherapy was similarly infrequently used - in 36.9% of the patients. Approximately 71% of the patients had used non-biologic systemic therapy before their law suit. No patients had contraindications, or were using drugs with problematic interactions, that would have prevented the use of all recommended systemic agents (cyclosporine, methotrexate, and acitretin). Given that guideline adherence requires use topical and systematic therapy before beginning biologic use, only 34 patients (16.7%) met guideline requirements.

Table 2 – Treatment prior to initiating law suit for biologic use.

	adalimumab 14 (6.9)	efalizumab 43 (21.2)	etanercept 35 (17.2)	infliximab 111 (54.7)	Total 203 (100)
Therapies					
None	1 (7.1)	12 (27.9)	6 (17.1)	25 (22.5)	44 (21.7)
Only Topical	0	0	0	0	0
Only Phototherapy	0 (0.0)	5 (11.6)	3 (8.7)	7 (6.3)	15 (7.4)
Only N-BIOSYS#	10 (71.4)	2 (4.6)	12 (34.3)	36 (32.4)	60 (29.6)
Combination of Therapies prior use of Biologic n (%)					
Topical+ Phototherapy	0	0	0	0	0
Topical + N-BIOSYS#	1 (7.1)	4 (9.3)	3 (8.6)	16(14.4)	24 (11.8)
Phototherapy + N-BIOSYS#	2 ()	18 (41.8)	8 (22.8)	22 (19.8)	50 (24.6)
Topical+Phototherapy+N-BIOSYS#	0 (0.0)	2 (4.6)	3 (8.6)	5 (4.5)	10 (4.9)
Recommended use of the biological agents according guidelines (7-10) n (%)					
Topical + N-BIOSYS	1 (7.1)	6 (14.0)	6 (17.1)	21 (18.9)	34 (16.7)

acitretin, metothrexate; ciclosporine; sd – standard deviation; PSO – psoriasis
acitretin, metothrexate; ciclosporin; sd – standard deviation; N-BIOSYS – non biologic systemic agents

Table 3 presents findings in the 91 patients who were still using a biologic agent at the time of the interview. The pattern of prior use was similar to the overall group, with 19.3% of patients having used both a topical agent and systemic therapy. All patients had visited a doctor at least once a year, but 25.2% did not undergo the recommended laboratory tests (blood count, differential count, liver function) (Table 3). Thus, only 14.2% of the patients met guideline criteria for both use of prior agents and appropriate monitoring.

Of the 203 respondents 134 (66%) perceived that they experienced important improvement with use of biologic agents, although 20 patients reported a deterioration they attributed to the biologic agents. Adverse effects severe enough to discontinue medication were reported by 23 patients (11.3%).

Table 3 - Clinical follow up and outcome judgment in patient with psoriasis still taking biologic agent.

Outcomes	adalimumab 9 (9.9)	etanercept 22 (62.9)	infliximab 60 (54.0)	Total 91(100)
Annual Review				
A *consults**	9 (100)	22 (100)	60 (100)	91(100)
B *laboratorial exams***	7 (77.8)	15 (68.2)	46 (76.7)	68 (74.8)
Clinical monitoring adequate				
C *A + B*	7 (77.8)	15 (68.9)	46 (76.4)	68 (74.8)
Therapies				
None	0 (0.0)	3 (13.6)	14 (23.3)	17 (18.7)
Only Topical	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Only Phototherapy	0 (0.0)	1 (4.5)	4 (6.7)	5 (5.5)
Only N-BIOSYS#	7 (77.8)	9 (40.9)	18 (30.0)	34 (37.4)
Combination of Therapies prior use of Biologic n (%)				
Topical + Phototherapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
D *Topical + N-BIOSYS#*	1 (11.1)	3 (13.6)	8 (13.3)	12 (13.2)
Phototherapy + N-BIOSYS#	1 (11.1)	4 (18.2)	13 (21.7)	18 (19.8)
E *Topical+Phototherapy+N-BIOSYS*	0 (0.0)	2 (9.1)	3 (5.0)	5 (5.5)
F Recommended use of the biological agents according guidelines				
D + E	1 (11.1)	5 (22.7)	11 (18.3)	17 (19.3)
Adherence of guideline				
*Prior drugs and monitoring (**C + D**)*	1 (11,1)	3 (13.6)	9 (15.0)	13 (14.2)

**at least one annual medical consult; blood differential (complete blood cell count), liver function tests;*

 # use of biologic agent after treatment with topic and one systemic non biologic agent;

DISCUSSION

Main Findings

The key finding of this investigation is that very few patients obtaining payment for use of biologic agents for treatment of psoriasis had met guideline criteria for use of non-biologic therapy prior to commencing expensive and potentially toxic biologic agents (Tables 2 and 3). In particular, topical agents had seldom been used in these patients. In addition, approximately 30% had not used any non-biologic systemic agents. Further, of those still using biologic agents approximately 25% had not undergone the recommended laboratory investigations in the prior year. Thus, complete adherence to guideline recommendations for

prior therapy occurred in only 16.7% of patients and complete guideline adherence including prior therapy and laboratory monitoring in only 14.2% of those still using biologic agents (Tables 2 and 3).

The patients in this sample did not have heart NYHA III / IV heart disease, a potential contraindication for TNFs (Table 1). However, the prevalent comorbidities detected in these patients involve the cardiovascular system, the main contraindication to the use of biological drugs (22). Thus, the pattern of comorbidity raises further concern regarding the use of biologic agents without, in approximately 30%, the prior use of non-biologic immunosuppressant therapy.

Strengths and weaknesses of the study

Strengths of this study include our ability to obtain a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis. We were able to contact and obtain consent from 203 or 218 potentially eligible patients. We obtained pharmacy records of medication use and corroborating information from patient interviews. Duplicate review of interview recordings ensured accurate information. We surveyed a number of key guidelines including both public agencies and specialty societies from a number of countries and used as criteria only recommendations included in all the guidelines.

Possible limitations in our study include the possibility that patient's memory of prior medication use may not have been accurate. In particular, approximately 20% of patients reported no prior topical, phototherapy, or system therapy prior to use of biologic agents. The interviews, however, included detailed descriptions of medications, including topical agents, and patients' failure to remember the use of topical agents may be implausible. We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents, and these data are therefore suspect.

Also we did not study the management of patients who have received biologics through the usual health care system (i.e. without recourse to the courts) represents another limitation of the study Thus, our study provides only indirect evidence regarding how these patients are managed within the Brazilian system".

Relation to evidence and recommendations

The guidelines we reviewed were consistent in their recommendation that patients with severe psoriasis who do not respond or have a contraindication to or are intolerant to topical therapy and systemic therapy with immunosuppressant, including cyclosporine and methotrexate, are candidates for biologic therapies [5-8 15]. The guidelines also recommended phototherapy as an alternative. Despite evidence of the cost-effectiveness of phototherapy in moderate-to-severe psoriasis [19 20], guidelines did not insist on a trial of phototherapy before treatment with biologic agents. .

Biologic agents may be associated with serious adverse effects, including an increase in the risk of malignancies opportunistic fungal infection, and lymphoma [10-12]. A particular concern is the use of drugs over the long term. Current the data available is insufficient to draw clear and reliable conclusions about either the efficacy of long-term treatments or the frequency of adverse effects over the long term [21-23]. The majority of plaintiffs are using biologics for over a year, and more than 10% for over three years, raising another possible concern.

Implications.

Biologic agents are not included in Brazilian official guideline to treat psoriasis. Therefore, access to this medication is largely from prescriptions by private practioners. Having obtained a prescription for a biologic agent, Brazilian citizen can launch legal action to have the government pay for the high cost medication. It is perhaps ironic that despite the last report of the Brazilian health assessment technology committee (Conitec) choosing to not recommend (1) the use of these biological drugs in the treatment of psoriasis primarily because of safety concerns, judicial decisions in favor of their use requires the public health system to provide funding.

One could argue that it may be unreasonable to ask judges to be aware of medical guidelines, particularly those arising from other jurisdictions. A proposed solution to this problem would be to provide the court with high quality technical analyses. In this case, experts in psoriasis aware of the guidelines would provide the analyses. So far, such analyses are unavailable [24-26]. Our results emphasize the need for technical analyses to guide court decisions, ideally considering two independent opinions.

Irrespective of issues of whether governments should fund biologics in psoriasis at all, clinical practice and judicial decisions should be consistent with highly credible international guidelines. Our results show an important gap between clinical practice and judicial

decisions in treatments prescribed to plaintiffs demanding medicines for Psoriasis in São Paulo, Brazil and corresponding guidelines.

Explanations for inappropriate practice include inadequate training and knowledge of the physicians who prescribe the drugs[27 28]. Another possibility is that incentives from the pharmaceutical industry are influencing the prescription of biologic agents in psoriasis. Whatever the reason, our findings demonstrate that the court system is not functioning well. This is not necessarily the fault of the judges, but of a system that does not ensure that judges have the appropriate access to expert guidance. Independent review by disinterested experts would have led the court to insist on appropriate prior treatment before considering biologic agents. The health system also appears negligent in not ensuring optimal follow-up to patients who receive payment for their drugs from the government. The responsibility for informing practitioners of optimal management could rest with the pharmaceutical industry, the national dermatologic society, or the government.

Our results suggest changes at both the level of clinical practice and the function of the judicial system are urgently needed.

What is already known on this subject?

Guidelines specify the circumstances in which biologic agents should be used in patients with psoriasis and the monitoring such patients should undergo. The extent to which clinicians follow these guidelines in a variety of clinical situations remains uncertain.

What this study adds?

In Brazil, major discrepancies exist between the management of patients who receive funding for biologic agents from the government through lawsuits and the management guidelines recommend. The majority of patients have not had the appropriate trials of less toxic drugs, and laboratory monitoring is suboptimal in approximately 25% of patients.

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Competing interests: none.

Data Sharing Statement: No additional data available.

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✓ **TITLE: Adherence to guidelines in use of biological agents to treat psoriasis in Brazil**

ABSTRACT

[BACKGROUND]: In São Paulo, Brazil, patients gain funding for biological agents for treatment of psoriasis through lawsuits to the government. The extent to which management of such patients adhere to authoritative guidelines is uncertain.

[OBJECTIVE]: To determine the extent to which clinical practice adheres to authoritative guidelines in patients receiving treatment for psoriasis through lawsuits.

[METHODS]: We identified patients through records of the State Health Secretariat of São Paulo from 2004 to 2011. We consulted guidelines from five countries and chose as standards only those recommendations that the guidelines uniformly endorsed. Pharmacy records provided data regarding biologic use. Guidelines recommended biologics agents only in patients with severe psoriasis who have failed to respond to both topical and systemic therapies (e.g. cyclosporine and methotrexate) and recommended yearly monitoring of blood counts and liver function.

[RESULTS]: Of 218 patients identified in the database, 3 did not meet eligibility criteria and 12 declined participation. Of 203 patients interviewed, 91 were still using biological medicine; we established adherence to laboratory monitoring in these patients. In the total sample, management failed to meet standards of prior use of topical and systemic medication in 169 (83.2%) of the patients. .Of the 91 patient using biological medicine at the time of the survey, 23 (25.2%) did not undergo appropriate laboratory tests.

[CONCLUSIONS]: Important discrepancies exist between clinical practice and the recommendations of guidelines the management of plaintiffs using biologic drugs to treat psoriasis.

Strengths and limitations

1. Strengths of this study include our ability to obtain a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis.
2. We obtained pharmacy records of medication use and corroborating information from patient interviews.
3. Duplicate review of interview recordings ensured accurate information.
4. Possible limitations in our study include the possibility that patients memory of prior medication use may not have been accurate.
5. The interviews, however, included detailed descriptions of medications, including topical agents, and patients' failure to remember the use of topical agents may be implausible.
6. We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents, and these data are therefore suspect.
7. We did not study the management of patients who have received biologics through the usual health care system.

INTRODUCTION

Psoriasis, chronic inflammatory immune-mediated skin disease that predominantly affects the skin and joints occurs in between 1.5 to 3% of the population[1]. Onset may occur at any age but peaks in the second and third decades. The severity of psoriasis varies widely, and its course is characterized by relapses and remissions, though it usually persists throughout life. Its negative impact on health-related quality of life is similar to that of ischemic heart disease, diabetes, depression and cancer [2].

The significant reduction in quality of life and the psychosocial disability suffered by patients highlight the need for prompt, effective treatment, and long-term disease control[3 4]. In mild psoriasis, topical treatment can be effective[5]. Those with moderate to severe disease often require treatment with phototherapy and systemic treatment[6]. When systemic traditional treatment with cyclosporine, methotrexate, or acitretin fail (non-biologic systemic agents or N-BISYS), systemic biological therapies such as the tumor necrosis factor antagonists' adalimumab, etanercept and infliximab, and the monoclonal antibody ustekimumab that targets interleukin-12 (IL-12) and IL-23 become options.[6-9].

Due to their immunosuppressive activity, some anti-TNFs have been associated with a small increased risk of infection in patients with psoriasis[10], and studies of TNF antagonist use in other disease areas have raised concerns over a potential link to cardiovascular side-effects, malignancies, and neurological defects[10-12]. Guidelines uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents.

In Brazil patients can, once they are prescribed by a clinician, go to the courts to force the state to pay for expensive medication such as biologics. Court decisions may not be consistent with optimal standards of care in terms of patients who are appropriate for use of biologics. Furthermore, once patients receive biologics through court decisions, subsequent management may not be optimal.

The objective of this study was to identify standards of management of psoriasis common to major international guidelines and to evaluate the extent to which Brazilian physicians who prescribed biologics that courts approved on the basis of law suits adhered to these standards.

METHODS

The protocol (cross-sectional design) was authorized by the State Department of Health (SES-SP) and also approved by the ethics committee for clinical research of University of Sorocaba on August 17, 2009, with protocol number 011/2009.

Choice of Guidelines and Guideline Recommendations

We consulted guidelines from the following countries: United Kingdom[13], Germany[7], Brazil,[9] United States[14], Canada[15] and European[16]. We used both national guidelines (NICE, SIGN)[5 6] and specialty society guidelines. We reviewed all recommendations in each guideline and chose as standards only those recommendations that for prior treatment were uniformly endorsed across all guidelines and for monitoring were endorsed by 4 of the 5 guidelines.

Recommendations uniformly endorsed by every guideline[5-9]specified that biologics should only be used in patients with severe psoriasis who had failed to respond to, have a contraindication to, or are intolerant of topical therapies, and at least one systemic therapy (e.g. cyclosporine or methotrexate). Guidelines also uniformly recommend at least one annual patient review to check for infections, malignancies, and other adverse effects of biologics agents and also to evaluate control of psoriasis. Guidelines specified that the review should include monitoring of complete blood cell count and liver function tests.

Eligibility Criteria

Patients were eligible if they had, through lawsuits filed against the state of São Paulo in the period 2004-2010, gained access to biologics for treatment of psoriasis. All patients gave informed consent.

Identification of Patients and Collection of Patient Data

In order to identify eligible patients, two researchers abstracted data from all the dispensing orders in the database for psoriasis - identified by ICD code L40 - originating from lawsuits from 2004-2010 including the name, address and telephone number, gender, age, healthcare provider, whether that provider worked in the public or private system, type of biologic dispensed, and diagnoses. We excluded patient with arthritis psoriatic.

We contacted patients with psoriasis by telephone, and if they proved eligible and agreed to participate in the study, conducted interviews. The interviews were conducted by telephone using Computer Assisted Telephonic Interviews (ITAC) technology with a microcomputer handset with headphones. This system allows recording and monitoring of the duration of the conversation [17 18]. Research staff working in pairs independently recorded data from the interviews, with discrepancies resolved by the principle investigator (LL).

The interview schedule was developed in consultation with a local dermatologist (see **Appendix)** after consideration of the recommendations consistent across guidelines. An electronic form was developed in Microsoft Office Access based on the instrument developed for the interviews. To address the items listed in the instrument, 16 screens were designed to record the data from the interviews. Each interviewer received training on use of language related to each question in the interview schedule. The questionnaire included the following: what drugs the patient was using for the treatment of psoriasis prior to the court judgment, the time of diagnosis of psoriasis, comorbidities and whether patients received at least annual review. For patients still taking biologics we determined if they had received a medical consultation in the previous year and what tests had been undertaken in the previous year. In Brazil, patients receive records of all their laboratory tests and typically retain these records indefinitely; all patients still receiving biologics reported that they had retained records of all of laboratory tests undertaken during the previous year.

Patients' report of the period in which they used the biologics were cross-checked with data obtained from pharmacy records and from legal records form lawsuits. Legal records form lawsuits gave us the name of patients, name of the drugs obtained through the law suit, whether the prescription came from private or public insurance, sex, diagnostic and age of patients. If we found discrepancy between the three sources of information, we considered the information from pharmacy records definitive. Thus, definitive information about the name of the biologic and the duration of use of the biologic was obtained from the pharmacy, and definitive information of the time of diagnosis, use of previous medicines, and laboratory results was obtained from the patient. We considered guideline adherence adequate when court decisions and subsequent clinical care had adhered to all recommendations from guidelines.

In the interviews we also asked patients about their adverse effects and whether these led to discontinuing medications and their perception of the effectiveness of the biologic agents.

RESULTS

We reviewed 25,184 lawsuits that had succeeded in obtaining medicines, dietary supplements, or other health products, such as orthotics and prosthetics, and diagnostic and therapeutic procedures in the period deposited in the Public Finance Courts Capital in period 2004 to 2010. Of 218 patients identified as using biologics for psoriasis, in 3 the contact information was a law office that did not allow us to contact patients, 1 patient had died, 2 had never used the biologic that was mandated by the court decision, and 9 refused the interview. We interviewed 203 patients, of whom 91 (44.8%) were still using a biologic agent (Figure 1).

Eligible patients received one of four biologic drugs: adalimumab, etanercept, infliximab and efalizumab. Table 1 presents the socio demographic and medical health characteristics of the 203 eligible patients as well as the duration patients used the biologic agents granted payment by the courts. Over a third of the patients used the biologic agents for less than a year, and over 50% for 1 to 3 years.

Table 1 - Baseline characteristics of plaintiffs with psoriasis

	Patients N=203	%
City of residence		
São Paulo	122	60
Other	81	40
Health care		
Private	141	69.5
Sex		
Male	*129*	*63.5*
Age (years)		
19 - 59	156	76.9
≥ 60	47	23.1
mean ± sd		48.9 ± 13.7
Time of diagnosis (years previous)		
6 or more	177	84.9
2 - 5	25	10.2
≤1 year	1	0.5
Comorbidities		
None	128	63
Cardiovascular disease	26	12.8
Diabetes mellitus	12	5.9
Others	37	18.2
Duration of use of biologic (months)		
12 or less	69	34.0
13 to 36	110	54.2
37 to 72	24	11.8

Sd= standard deviation

Table 2 presents the use of non-biologic medications prior to the law suit decision to pay for the use of a biologic agent. Over 20% of the patients had not used any conventional interventions - either topical, light, or systemic agents - for psoriasis prior to launching their law suit for use of biologic agents. Topical agents were used very infrequently - in only approximately 16% of patients. Phototherapy was similarly infrequently used - in 36.9% of the patients. Approximately 71% of the patients had used non-biologic systemic therapy before their law suit. No patients had contraindications, or were using drugs with problematic interactions, that would have prevented the use of all recommended systemic agents (cyclosporine, methotrexate, and acitretin). Given that guideline adherence requires use topical and systematic therapy before beginning biologic use, only 34 patients (16.7%) met guideline requirements.

Table 2 – Treatment prior to initiating law suit for biologic use.

	adalimumab 14 (6.9)	efalizumab 43 (21.2)	etanercept 35 (17.2)	infliximab 111 (54.7)	Total 203 (100)
Therapies					
None	1 (7.1)	12 (27.9)	6 (17.1)	25 (22.5)	44 (21.7)
Only Topical	0	0	0	0	0
Only Phototherapy	0 (0.0)	5 (11.6)	3 (8.7)	7 (6.3)	15 (7.4)
Only N-BIOSYS#	10 (71.4)	2 (4.6)	12 (34.3)	36 (32.4)	60 (29.6)
Combination of Therapies prior use of Biologic n (%)					
Topical+ Phototherapy	0	0	0	0	0
Topical + N-BIOSYS#	1 (7.1)	4 (9.3)	3 (8.6)	16(14.4)	24 (11.8)
Phototherapy + N-BIOSYS#	2 ()	18 (41.8)	8 (22.8)	22 (19.8)	50 (24.6)
Topical+Phototherapy+N-BIOSYS#	0 (0.0)	2 (4.6)	3 (8.6)	5 (4.5)	10 (4.9)
Recommended use of the biological agents according guidelines (7-10) n (%)					
Topical + N-BIOSYS	1 (7.1)	6 (14.0)	6 (17.1)	21 (18.9)	34 (16.7)

acitretin, metothrexate; ciclosporine; sd – standard deviation; PSO – psoriasis
acitretin, metothrexate; ciclosporin; sd – standard deviation; N-BIOSYS – non biologic systemic agents

Table 3 presents findings in the 91 patients who were still using a biologic agent at the time of the interview. The pattern of prior use was similar to the overall group, with 19.3% of patients having used both a topical agent and systemic therapy. All patients had visited a doctor at least once a year, but 25.2% did not undergo the recommended laboratory tests (blood count, differential count, liver function) (Table 3). Thus, only 14.2% of the patients met guideline criteria for both use of prior agents and appropriate monitoring.

Of the 203 respondents 134 (66%) perceived that they experienced important improvement with use of biologic agents, although 20 patients reported a deterioration they attributed to the biologic agents. Adverse effects severe enough to discontinue medication were reported by 23 patients (11.3%).

Table 3 - Clinical follow up and outcome judgment in patient with psoriasis still taking biologic agent.

Outcomes	adalimumab 9 (9.9)	etanercept 22 (62.9)	infliximab 60 (54.0)	Total 91(100)
Annual Review				
A *consults**	9 (100)	22 (100)	60 (100)	91(100)
B *laboratorial exams***	7 (77.8)	15 (68.2)	46 (76.7)	68 (74.8)
Clinical monitoring adequate				
C *A + B*	7 (77.8)	15 (68.9)	46 (76.4)	68 (74.8)
Therapies				
None	0 (0.0)	3 (13.6)	14 (23.3)	17 (18.7)
Only Topical	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Only Phototherapy	0 (0.0)	1 (4.5)	4 (6.7)	5 (5.5)
Only N-BIOSYS#	7 (77.8)	9 (40.9)	18 (30.0)	34 (37.4)
Combination of Therapies prior use of Biologic n (%)				
Topical + Phototherapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
D *Topical + N-BIOSYS#*	1 (11.1)	3 (13.6)	8 (13.3)	12 (13.2)
Phototherapy + N-BIOSYS#	1 (11.1)	4 (18.2)	13 (21.7)	18 (19.8)
E *Topical+Phototherapy+N-BIOSYS*	0 (0.0)	2 (9.1)	3 (5.0)	5 (5.5)
F Recommended use of the biological agents according guidelines				
D + E	1 (11.1)	5 (22.7)	11 (18.3)	17 (19.3)
Adherence of guideline				
*Prior drugs and monitoring (**C + D**)*	1 (11,1)	3 (13.6)	9 (15.0)	13 (14.2)

**at least one annual medical consult; blood differential (complete blood cell count), liver function tests;*

 # use of biologic agent after treatment with topic and one systemic non biologic agent;

DISCUSSION

Main Findings

The key finding of this investigation is that very few patients obtaining payment for use of biologic agents for treatment of psoriasis had met guideline criteria for use of non-biologic therapy prior to commencing expensive and potentially toxic biologic agents (Tables 2 and 3). In particular, topical agents had seldom been used in these patients. In addition, approximately 30% had not used any non-biologic systemic agents. Further, of those still using biologic agents approximately 25% had not undergone the recommended laboratory investigations in the prior year. Thus, complete adherence to guideline recommendations for

prior therapy occurred in only 16.7% of patients and complete guideline adherence including prior therapy and laboratory monitoring in only 14.2% of those still using biologic agents (Tables 2 and 3).

The patients in this sample did not have heart NYHA III / IV heart disease, a potential contraindication for TNFs (Table 1). However, the prevalent comorbidities detected in these patients involve the cardiovascular system, the main contraindication to the use of biological drugs (22). Thus, the pattern of comorbidity raises further concern regarding the use of biologic agents without, in approximately 30%, the prior use of non-biologic immunosuppressant therapy.

Strengths and weaknesses of the study

Strengths of this study include our ability to obtain a complete list of all individuals who succeeded in obtaining government payment for biologic agents for psoriasis. We were able to contact and obtain consent from 203 or 218 potentially eligible patients. We obtained pharmacy records of medication use and corroborating information from patient interviews. Duplicate review of interview recordings ensured accurate information. We surveyed a number of key guidelines including both public agencies and specialty societies from a number of countries and used as criteria only recommendations included in all the guidelines.

Possible limitations in our study include the possibility that patient's memory of prior medication use may not have been accurate. In particular, approximately 20% of patients reported no prior topical, phototherapy, or system therapy prior to use of biologic agents. The interviews, however, included detailed descriptions of medications, including topical agents, and patients' failure to remember the use of topical agents may be implausible. We did not obtain corroboration of reports of adverse effects or apparent improvement with the biologic agents, and these data are therefore suspect.

Also we did not study the management of patients who have received biologics through the usual health care system (i.e. without recourse to the courts) represents another limitation of the study Thus, our study provides only indirect evidence regarding how these patients are managed within the Brazilian system".

Relation to evidence and recommendations

The guidelines we reviewed were consistent in their recommendation that patients with severe psoriasis who do not respond or have a contraindication to or are intolerant to topical therapy and systemic therapy with immunosuppressant, including cyclosporine and methotrexate, are candidates for biologic therapies [5-8 15]. The guidelines also recommended phototherapy as an alternative. Despite evidence of the cost-effectiveness of phototherapy in moderate-to-severe psoriasis [19 20], guidelines did not insist on a trial of phototherapy before treatment with biologic agents. .

Biologic agents may be associated with serious adverse effects, including an increase in the risk of malignancies opportunistic fungal infection, and lymphoma [10-12]. A particular concern is the use of drugs over the long term. Current the data available is insufficient to draw clear and reliable conclusions about either the efficacy of long-term treatments or the frequency of adverse effects over the long term [21-23]. The majority of plaintiffs are using biologics for over a year, and more than 10% for over three years, raising another possible concern.

Implications.

Biologic agents are not included in Brazilian official guideline to treat psoriasis. Therefore, access to this medication is largely from prescriptions by private practioners. Having obtained a prescription for a biologic agent, Brazilian citizen can launch legal action to have the government pay for the high cost medication. It is perhaps ironic that despite the last report of the Brazilian health assessment technology committee (Conitec) choosing to not recommend (1) the use of these biological drugs in the treatment of psoriasis primarily because of safety concerns, judicial decisions in favor of their use requires the public health system to provide funding.

One could argue that it may be unreasonable to ask judges to be aware of medical guidelines, particularly those arising from other jurisdictions. A proposed solution to this problem would be to provide the court with high quality technical analyses. In this case, experts in psoriasis aware of the guidelines would provide the analyses. So far, such analyses are unavailable [24-26]. Our results emphasize the need for technical analyses to guide court decisions, ideally considering two independent opinions.

Irrespective of issues of whether governments should fund biologics in psoriasis at all, clinical practice and judicial decisions should be consistent with highly credible international guidelines. Our results show an important gap between clinical practice and judicial

decisions in treatments prescribed to plaintiffs demanding medicines for Psoriasis in São Paulo, Brazil and corresponding guidelines.

Explanations for inappropriate practice include inadequate training and knowledge of the physicians who prescribe the drugs[27 28]. Another possibility is that incentives from the pharmaceutical industry are influencing the prescription of biologic agents in psoriasis. Whatever the reason, our findings demonstrate that the court system is not functioning well. This is not necessarily the fault of the judges, but of a system that does not ensure that judges have the appropriate access to expert guidance. Independent review by disinterested experts would have led the court to insist on appropriate prior treatment before considering biologic agents. The health system also appears negligent in not ensuring optimal follow-up to patients who receive payment for their drugs from the government. The responsibility for informing practitioners of optimal management could rest with the pharmaceutical industry, the national dermatologic society, or the government.

Our results suggest changes at both the level of clinical practice and the function of the judicial system are urgently needed.

What is already known on this subject?

Guidelines specify the circumstances in which biologic agents should be used in patients with psoriasis and the monitoring such patients should undergo. The extent to which clinicians follow these guidelines in a variety of clinical situations remains uncertain.

What this study adds?

In Brazil, major discrepancies exist between the management of patients who receive funding for biologic agents from the government through lawsuits and the management guidelines recommend. The majority of patients have not had the appropriate trials of less toxic drugs, and laboratory monitoring is suboptimal in approximately 25% of patients.

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Contributors: LL, IC, SBF and COC had the original idea and they developed the study protocol. GG, LL, MS and COC performed data analysis and drafted the manuscript. MS, FSDF, SBF, MCC and IC contributed to data collection. All authors contributed to the preparation of the manuscript and read and approved the final version.

Competing interests: none.

Ethics approval: this study is part of PSAR Project approved by committee for clinical research of University of Sorocaba on August 17, 2009, with protocol number 011/2009.

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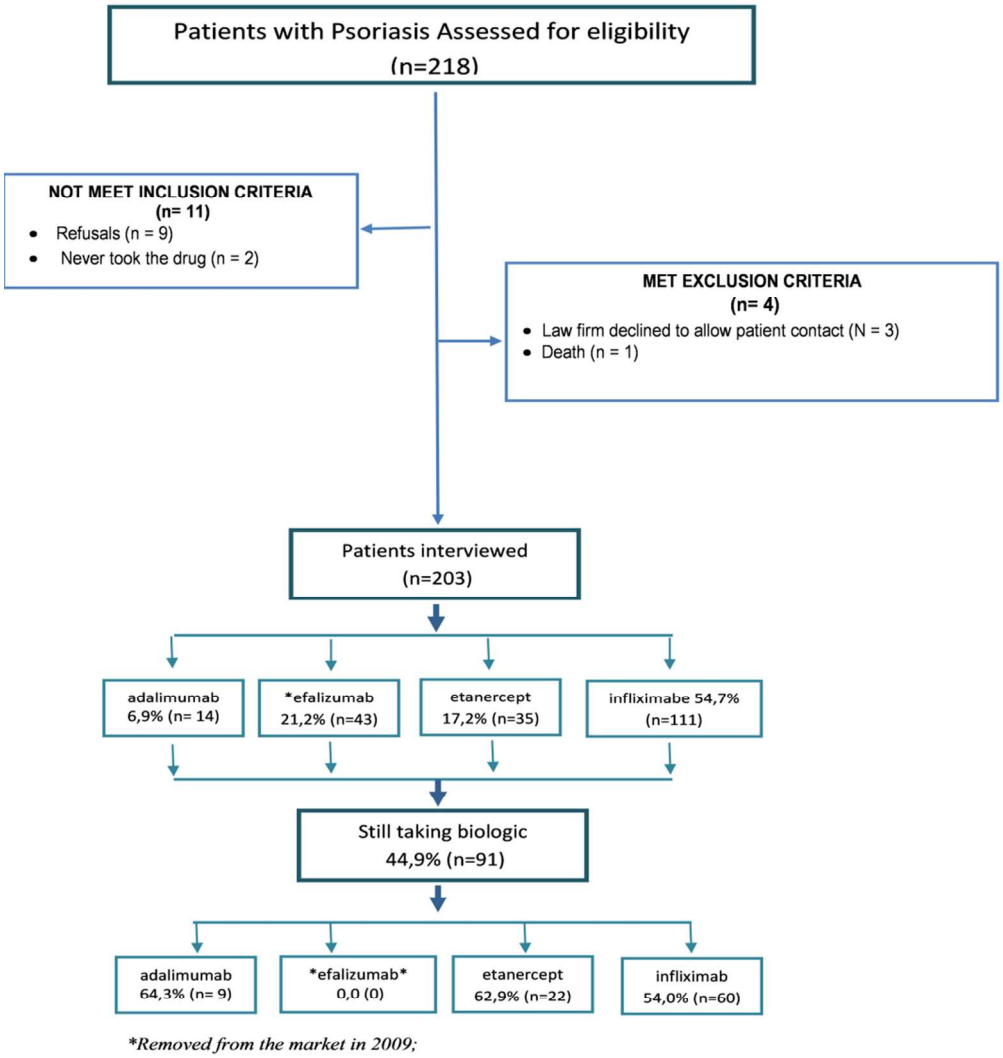

Figure 1 – Flow diagram of the steps of the sample composition of plaintiff included in the study

90x107mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	*6*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	FIGURE 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	TABLE 1, PAGE 8
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9, 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	9, 10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.