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Evaluation of Information on Pregnancy and Lactation in Patient Information Leaflets of Antirheumatic Drugs

Nesrin ÇAĞLAYAN DUMAN[1*]
Nevsun İNANÇ[2]
Atila KARAALP[3]

[1]Department of Medical Pharmacology, Faculty of Medicine, Ordu University, Ordu, Turkiye
[2]Department of Internal Medicine, Faculty of Medicine, Marmara University, Istanbul, Turkiye
[3]Department of Medical Pharmacology, Faculty of Medicine, Biruni University, Istanbul, Turkiye

ABSTRACT

Objective: The use of antirheumatic drugs during pregnancy and lactation should be arranged so as not to harm the fetus and mother. There are various sources of information, such as pregnancy guidelines and patient information leaflet (PIL), which are used to determine the course of treatment during these periods.
Methods: In this study, different antirheumatic drug PILs were evaluated in terms of the inconsistency of their information on the use of drugs during pregnancy and lactation with the current European League Against Rheumatism (EULAR)' guidelines. Inconsistent PILs were categorized into 2 different groups according to their information on the use of the drug during pregnancy and lactation: I. lack of information and II. Conflict or contrary of information.
Results: It was found that 72.1% of the 179 PILs had inconsistent pregnancy information (lack of information n=22, conflict or contrary of information n=107) and 75.4% had inconsistent lactation information (lack of information n=22, conflict or contrary of information n=113) compared with EULAR. According to the EULAR, 79.3% (n=142) of the drugs in this study were suitable for use in pregnancy and 80.4% (n=144) were suitable for use during lactation.
Conclusion: The findings of this study draw attention to the need for national and international regulation to harmonize the information in PILs with the current literature. This study will be useful for patients and healthcare professionals to ensure that PILs are compatible with the current literature.

Key words: Antirheumatic drug, Lactation, Patient information leaflet, Pregnancy.

Introduction

Rheumatic diseases are more likely to affect women of childbearing age (Giles et al., 2019). Pregnant women with rheumatic diseases are at higher risk of maternal and neonatal complications than the general pregnant population (He & Wei, 2020; Sim et al., 2023). These patients may become pregnant while taking drug or may need to take drug during pregnancy and/or lactation. For a healthy pregnancy, the drug status of these patients should be adjusted before pregnancy, such as discontinuing known or potentially teratogenic drugs and/or switching to appropriate drugs. On the other hand, the control of disease activity in rheumatic diseases should be performed carefully during pregnancy and lactation. Drugs used in the treatment of rheumatological diseases known to be compatible with pregnancy and lactation should be given to the mother at the lowest possible dose, with the aim of avoiding harm to the fetus and baby (Brooks & Needs, 1990).

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Corresponding author: Nesrin Çağlayan Duman
E-mail: nesrincglyndmn@gmail.com
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Guidelines and recommendations about antirheumatic drug use in pregnancy and lactation are periodically published which became scientific sources that enable healthcare professionals and patients to access up-to-date information. The European League Against Rheumatism (EULAR) has compiled available data on antirheumatic drugs from the literature and various databases and has developed an expert consensus on the compatibility of these drugs during pregnancy and lactation, and considerations for their use during these periods (Götestam Skorpen et al., 2016). There are differences between these sources of information on drug use in pregnancy in terms of the usability of drugs (Birru Talabi & Clowse, 2020; Flint et al., 2016).

In a study of patients with rheumatic diseases, 84% of patients reported receiving information about the drug from patient information leaflets (PILs), 80% from rheumatologists and 50% from general practitioners (Ørnbjerg et al., 2008). However, the information given by guidelines and authorities may sometimes contradict by the information supplied by PILs. Lack of up-to-date information concerning the use of antirheumatic drugs during pregnancy and lactation may lead to unable to manage the treatment that leads to unnecessary discontinuation or switching of drugs (Desai et al., 2016; Flint et al., 2016).

As in the whole world, there is a PIL in every pharmaceutical preparation in Turkiye including the antirheumatic drugs, for giving essential information about the drugs to the patients. Those PILs include pharmaceutical contents, therapeutic indications, contraindications, precautions, how it is used, possible side effects, storage conditions, contents of the package and some other related information in Turkiye (Turkish Medicines and Medical Devices Agency, 2008).

In this study, different antirheumatic drug PILs were evaluated for inconsistencies in their information on the use of the drugs during pregnancy and lactation with the current EULAR recommendations.

Methods

This study compares the EULAR recommendations on the use of antirheumatic drugs in the period of pregnancy and lactation, published by the EULAR Task Force in 2016, with the information provided in the PILs of antirheumatic drugs (originator and generics, if available) approved in Turkey. The PILs were obtained from the website of the Turkish Medicines and Medical Devices Agency (TITCK), the Turkish national official regulatory authority for medicines and medical devices. Only the PILs of the antirheumatic drugs approved in Turkiye (both originator and generics) have been included in this study. Additionally, the preparations which have only those antirheumatic agents were included and any combination of those agents were excluded in this study. Likewise, topically administered preparations were also excluded. Orally or parenterally administered antirheumatic preparations' PILs were evaluated.

In this study, the PILs were classified into 3 different groups according to the information they provided on the use of the drug in the period of pregnancy and lactation, as follows: I. lack of information, II. conflict or contrary information and III. consistent with EULAR recommendations. Thus, the PILs included in the first and second group are accepted as having inconsistencies and the details of inconsistencies between the EULAR recommendations and PILs were:

Although EULAR recommendations indicate that the use of drug is compatible during pregnancy and lactation but if the PILs:

a) if there is a warning such as "Before using this drug, tell your doctor if you are pregnant, trying to become pregnant, or are lactating", "Consult your doctor or pharmacist before using the drug" and "If you notice that you are pregnant during your treatment, consult your doctor or pharmacist immediately" or

b) did not state any definite recommendation about the agent's use during pregnancy and lactation even it is expressed as "human and/or animal data identifies transplacental passage, excretion into breast milk or cause adverse outcome" (accepted as "type I inconsistency").

Although EULAR recommendations indicate the use of drug is compatible during pregnancy and lactation, but the PIL restricts, contraindicates or not recommends the use during pregnancy and lactation (accepted as "type II inconsistency").

We also evaluated the PILs of antirheumatic pharmaceutical preparations that were approved by TITCK before or after the publishing date of EULAR recommendations which was 17 February 2016. PILs and EULAR recommendations were reviewed by both authors (N.C.D., A.K.). The study examined interrater consensus by calculating Cohen's kappa coefficient. The third author

(N.I.) was the decision-maker in cases of disagreement between the other authors. Descriptive statistics and kappa coefficient calculations were performed using Microsoft Excel 2024 software for statistical analysis.

Results

Inter-rater agreement

Cohen's kappa coefficient was calculated as 0.824 for pregnancy and 0.874 for lactation, indicating high inter-rater agreement. There were 28 PILs that could not be agreed between the two authors and these PILs were evaluated by the third author.

Agents

One hundred seventy nine PILs of antirheumatic preparations having 31 different pharmacologically active substances were analyzed: 4 nonsteroidal anti-inflammatory agents (aspirin, diclofenac, ibuprofen, naproxen), 1 selective COX-2 inhibitor (celecoxib), 3 glucocorticoids (methylprednisolone, prednisolone, prednisone), colchicine, 5 DMARDs (chloroquine, hydroxychloroquine, leflunomide, methotrexate, sulfasalazine), 5 immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, mycophenolate, tacrolimus,), intravenous immunoglobulin (IVIG), 10 biopharmaceutical agents (abatacept, adalimumab, belimumab, certolizumab, etanercept, infliximab, golimumab, rituximab, tocilizumab, ustekinumab), and tofacitinib.

Pregnancy information

Out of the 179 PILs, 72.1% presented information inconsistencies about the drugs' use during pregnancy. On the other hand, 27.9% of the PILs (n=50) have consistency. The PILs that have inconsistencies about the drugs' use during pregnancy period regarding EULAR recommendations are of acetyl salicylic acid, diclofenac, ibuprofen, naproxen, methylprednisolone, colchicine, prednisolone, prednisone, chloroquine, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus, intravenous immunoglobulin, adalimumab, etanercept, infliximab, rituximab and golimumab (20 out of 31 different agents).

The reasons for inconsistencies are the lack of information in 12.3% of the PILs (n=22) and 59.8% (n=107) where the information is in conflict with or contrary to the EULAR recommendations. Before EULAR, 71 PILs were issued. The reasons for inconsistencies are the lack of information in 16.9% of the PILs (n=12) and 57.8% (n=41) where the information is in conflict with or contrary to the EULAR recommendations. The amount of consistency is 25.3% of the PILs (n=18). After EULAR, 108 PILs were issued. The reasons for inconsistencies are the lack of information in 9.3% of the PILs (n=10) and 61.1% (n=66) where the information is in conflict with or contrary to the EULAR recommendations. The reasons for consistencies are 29.6% of the PILs (n=32). After the EULAR recommendations released in 2016, 108 of the 179 drugs were revised in their PILs or newly registered to the market and 4.3% become compliant, was shown in Table 1.

Table 1. Analysis of consistencies and inconsistencies between the EULAR recommendations and PILs for drug use during pregnancy and lactation

	Inconsistent				**Consistent**	
	Lack of information		**Conflict or contrary information**			
	Pregnancy n (%)	**Lactation** n (%)	**Pregnancy** n (%)	**Lactation** n (%)	**Pregnancy** n (%)	**Lactation** n (%)
All (n=179)	22 (12,3)	22 (12,3)	107 (59,8)	113 (63,1)	50 (27,9)	44 (24,6)
Before EULAR (n=71)	12 (16,9)	12 (16,9)	41 (57,8)	44 (62)	18 (25,3)	15 (21,1)
After EULAR (n=108)	10 (9,3)	10 (9,3)	66 (61,1)	69 (63,9)	32 (29,6)	29 (26,8)

EULAR: European League Against Rheumatism, PIL: Patient information leaflet

Some of the PILs of generic preparations of naproxen, prednisolone and tacrolimus had different information than the generics about pregnancy period, which was shown in Table 2.

Table 2. Classification of PILs compared to EULAR recommendations in 3 different groups according to their information during pregnancy

Consistent	Naproxen*, methotrexate, mycophenolate, cyclophosphamide, leflunomide, celecoxib, certolizumab, golimumab, abatacept, tocilizumab, belimumab, ustekinumab, tofacitinib
Lack of information	Ibuprofen, methylprednisolone, prednisolone*, tacrolimus*, intravenous immunoglobulin, rituximab
Conflict or contrary information to EULAR	Aspirin, diclofenac, ibuprofen, naproxen*, prednisolone*, prednisone chloroquine, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus*, colchicine, adalimumab, etanercept, infliximab

EULAR: European League Against Rheumatism, PIL: Patient information leaflet

*Some of the PILs of generic preparations of naproxen, prednisolone and tacrolimus had different information than the generics (i.e., the information of two of naproxen preparations' PILs were consistent with EULAR recommendations while remaining 25 PILs' information were conflicting regarding the drugs' use during pregnancy).

Drugs suitable for use in pregnancy

According to EULAR recommendations, 79.3% (n=142) of the drugs included in this study are suitable to use during pregnancy. There is clear information that only one-tenth of the PILs of these drugs (n=15), that are suitable for use during pregnancy are used during pregnancy.

Lactation information

When we focused on the information given by the PILs about the agents' use during lactation, 135 of 179 (75.4%) also have inconsistencies with the EULAR recommendations. The PILs that have inconsistencies about the drugs' use lactation period regarding EULAR recommendations are of acetyl salicylic acid, diclofenac, ibuprofen, naproxen, celecoxib, methylprednisolone, colchicine, prednisolone, prednisone, chloroquine, hydroxychloroquine, azathioprine, sulfasalazine, tacrolimus, cyclosporine, intravenous immunoglobulin, adalimumab, etanercept, infliximab, golimumab and tofasitinib (21 out of 31 different agents).

The reasons for inconsistencies are the lack of information in 12.3% of the cases (n=22) and 63.1% of cases (n=113) where the information is in conflict with or contrary to the EULAR recommendations. Before EULAR, 71 PILs were issued. The reasons for inconsistencies are the lack of information in 16.9% of the PILs (n=12) and 62% (n=44) where the information is in conflict with or contrary to the EULAR recommendations. The amount of consistency is 21.1% of the PILs (n=15). After EULAR, 108 PILs were issued. The reasons for inconsistencies are the lack of information in 9.3% of the PILs (n=10) and 63.9% (n=69) where the information is in conflict with or contrary to the EULAR recommendations. The amount of consistency is 26.8% of the PILs (n=29). After the EULAR recommendations released in 2016, 108 of the 179 drugs were revised in their PILs and 5.7% become compliant, was shown in Table 1.

Some of the PILs of generic preparations of naproxen, ibuprofen, prednisolone, and intravenous immunoglobulin had different information than the generics about lactation period was shown in Table 3.

Table 3. Classification of PILs compared to EULAR recommendations in 3 different groups according to their information during lactation

Consistent	Prednisone, methotrexate, mycophenolate, cyclophosphamide, leflunomide, intravenous immunoglobulin*, abatacept, belimumab, certolizumab, golimumab, rituximab, tocilizumab, tofacitinib
Lack of information	Ibuprofen*, naproxen*, methylprednisolone, prednisolone*, colchicine, intravenous immunoglobulin*, ustekinumab
Conflict or contrary information to EULAR	Aspirin, diclofenac, ibuprofen*, naproxen*, prednisolone*, celecoxib, chloroquine, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus, adalimumab, etanercept, infliximab

EULAR: European League Against Rheumatism, PIL: Patient information leaflet

*Some of the PILs of generic preparations of naproxen, ibuprofen, prednisolone, and intravenous immunoglobulin were having different information than the generics (i.e., the information of one of intravenous immunoglobulin preparation's PIL was consistent with EULAR recommendations while remaining 10 PILs' information were having lack of information regarding the drugs' use during lactation).

Drugs suitable for use in lactation

According to EULAR recommendations, 80.4% (n=144) of the drugs in this study are suitable for use in lactation. There is clear information that these drugs, which are suitable for use in lactation, were stated to be suitable for use during lactation in 6.9% (n=10) of PILs**.**

PIL active ingredients compatible with EULAR both during pregnancy and lactation

PILs (Originator and all generics, if any) that contain information compatible with EULAR in both pregnancy and lactation consist of methotrexate, mycophenolate, cyclophosphamide, abatacept, belimumab, leflunomide, tocilizumab, ustekinumab which should not be used during pregnancy and lactation and certolizumab that can be used during these periods (n=40, 22.3%).

There are 15 PILs in this study of methotrexate, mycophenolate mofetil and cyclophosphamide, which are known to be teratogenic and should be discontinued before pregnancy according to EULAR. The pregnancy and lactation information of these PILs is in line with EULAR.

Discussion

Little research has investigated the discrepancy between the PILs of antirheumatic drugs and the pregnancy and lactation information of scientific sources.

In the present study, we used the EULAR recommendations, which is a current source, to determine the differences in pregnancy and lactation information in PILs of antirheumatic drugs in Turkiye. Current study results revealed that only 27.9% of the PILs' pregnancy information contains current drug guidance information whereas the remaining 72.1% is inconsistent to EULAR recommendations. In another study performed in Argentina the inconsistency ratio was half of PILs as to pregnancy (Sabando et al., 2018). Although patients, guidelines and the drugs are the same, this shows that the information in the PILs' of antirheumatic preparations do not contain standard information against the countries. In a study comparing PIL and established clinical resources of 245 drugs, it was stated that 75.9% of pregnancy information and 87.3% of lactation information were inconsistent (Brown et al., 2016). In addition, the availability of pregnancy and lactation information in PIL varies from country to country (Arsalan et al., 2015; Hailu et al., 2022; Khamas et al., 2019).

The difference of this study is the evaluation of PILs according to the publication date of the scientific source. 39.7% (n=71) of the drugs in current study were approved for PIL before EULAR recommendations. When approved PILs were evaluated after the ER was published, PILs were found to be inconsistent at a rate of 71.4% during pregnancy and 73.2% during lactation. In current study, it was determined that after the publication of the EULAR recommendations, PIL compliance increased by 4.3% during pregnancy and 5.7% during lactation. This increase is not sufficient and PILs, which are one of the drug information sources of patients, should be updated by companies on the basis of scientific resources. The current study does not explain whether this increase is due to EULAR recommendations. Regulations in accordance with the guidelines are important in terms of patient compliance and trust in the health authority.

Most of the drugs in this study were compatible with pregnancy and lactation according to the EULAR recommendations (n=142 and n=144, respectively). It was determined that 89.4% of the drugs compatible with pregnancy did not have information compatible with pregnancy. This rate is 93.1% for lactation. In one study, it was stated that inconsistent information about pregnancy and lactation confuses patients (Bjerrum & Foged, 2003). The confusion caused by this inconsistency may lead to unnecessary drug discontinuation and cessation of lactation in rheumatology patients (Ince-Askan et al., 2019; Kemper et al., 2022; Rebić et al., 2020). There are studies showing that discontinuation of drugs in pregnant women with rheumatic disease causes exacerbation of the disease (Gerardi et al., 2022; van den Brandt et al., 2017).

In a study, it was stated that PILs containing the same active ingredient contain inconsistent information with each other and the guidelines (Crunkhorn et al., 2017). Also in this study, the fact that different preparations of the same active substance contain different information may cause patients to distrust health authority (naproxen, ibuprofen, prednisolone, tacrolimus, and intravenous immunoglobulin). A study showed that inconsistency and different information from different PILs involving the same active substance can lead to confusion among patients (Bjerrum & Foged, 2003). PILs containing different information on these drugs may reduce confidence in the health authority that approves them.

Precautions especially for pregnancy and lactation should be included in PILs, which are the most important document of information about a medicine that patients have access (Arsalan et al., 2015). 12.3% of the PILs in this study contain general information that does not mention the risk in pregnancy and lactation. According to the European Medicines Agency 2009 publication on consumer expectations, PILs should clearly describe the drug's benefits on the one hand and the drug's risks on the other, for pregnant women (European Medicines Agency, 2009).

The results of this study indicate that there is a national and international need for the information in the PIL to be in harmony with the current literature. Current study will be beneficial for patients and healthcare professionals to ensure that PILs are compatible with the current literature. Current study protocol can be developed and used in new studies where the pregnancy and lactation information of PILs related to different drug groups are compared with scientific sources.

This study has potential limitations. The first is to compare with a single scientific source (EULAR). The findings in the study were created because of personal evaluations. Although this seems like a limitation, we believe that the presence of a rheumatologist and two pharmacologists in the evaluation team who have studied drug use during pregnancy and lactation contributes to the analysis of the differences in the contents of PILs.

Conclusions and Recommendations

The information in the PILs of the drugs such as hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus, colchicine about the use of the drugs in some or all periods of pregnancy are either restricted or not recommended although they were expressed to be safe and compatible by the EULAR recommendations. Therefore, this situation has the potential to create a negative opinion against rheumatology specialists who follow the literature regularly, both in patients and non-specialist physicians.

The data we obtained from this study showed that for two-thirds of the pregnancy and lactation information (61.1% of pregnancy and 63.9% of lactation) in PILs of antirheumatic drugs had conflicting information with that in the EULAR recommendations. These differences can lead to ambiguity and potential risks, especially for patients and healthcare professionals. The findings obtained in the study indicate that there is a need for more guidance and standardization on the content of PIL information. Information must be compatible between regulatory agencies and scientific sources. According to the literature, the problem of heterogeneous drug information is not limited to Turkey and that current study results should be evaluated internationally.

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