Sex Differences in the Treatment of Psoriatic Arthritis: A Systematic Literature Review

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ABSTRACT: Psoriatic arthritis (PsA) is a chronic inflammatory condition associated with skin psoriasis and manifests a wide clinical phenotype, with proposed differences between sexes. Current treatments are based on traditional disease-modifying anti-rheumatic drugs (DMARD), and biologic agents and studies have reported different clinical response patterns depending on sex factors. We aimed to identify sex differences in drug retention rate in patients with PsA and performed a systematic research on MEDLINE, EMBASE and Cochrane databases (1979 to June 2015) for studies regarding effectiveness (measured as drug retention rate) in PsA in both traditional DMARDs and biologics. Demographic data as well as retention rates between sexes were extracted. From a total 709 retrieved references, we included 9 articles for the final analysis. Only one study reported data regarding DMARDs, while eight studies reported retention rate for anti-tumor necrosis factor (TNF) biologics, mainly infliximab, adalimumab and etanercept. No differences were reported in retention rates between sexes for methotrexate, while women manifested lower retention rates compared to men with regard to anti-TNF. We highlight the need to include sex differences in the management flow chart of patients with PsA.

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Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease that typically involves the synovial tissue, the entheses and the spine, in association with current psoriasis or a personal or family history of the skin condition. PsA belongs to the broader group of spondyloarthritides (SpA) which also include ankylosing spondylitis (AS), reactive arthritis, enteropathic arthritis, and undifferentiated spondyloarthritis [1]. These diseases share a strong genetic background, as represented by the association of AS with the HLA-B*27 allele, but unlike other rheumatic diseases there is no female preponderance or association with specific autoantibodies.

Recently, gender medicine has been receiving growing attention, namely, the study of how diseases differ between men and women in terms of diagnosis, clinical manifestations and therapeutic approach, with obvious implications for reproductive health. More importantly, research is moving to personalized medicine, a process that suggests the customization of health care tailored to every patient. Personalized medicine not only takes into account the sex of the patient, but may investigate his/her DNA for pharmacogenomics to tailor the individual most appropriate therapy for better cost-effectiveness. Nonetheless and different from rheumatoid arthritis, few studies have investigated the role of sex in the development of psoriatic disease, especially PsA.

PsA clinical manifestations vary widely to include peripheral arthritis, axial involvement, enthesitis and dactylitis. Earlier reports suggested that spondyloarthritides were predominant in men [2], but PsA is currently considered a disease equally affecting both sexes [3], with studies alternatively reporting male [4] or female [5] preponderance. Sex differences in PsA include a more frequent axial involvement in men [6] and a predominant peripheral arthritis with higher disability scores in women [7]. However, few studies have assessed the differences in clinical manifestations between sexes, especially in large cohorts of patients.

The treatment of PsA has been discussed in recent guidelines and recommendations and is based on non-steroidal anti-inflammatory drugs (NSAIDs), traditional disease-modifying anti-rheumatic drugs (DMARDs), particularly methotrexate (MTX), biologic agents blocking tumor necrosis factor-alpha (TNFα), interleukin (IL)-12/IL-23, IL-17, and most recently small molecules directed at phosphodiesterase-4 (anti-PDE4), which represent target therapies for key molecules involved in psoriatic disease pathogenesis [8-12]. Sex differences are seen in the outcomes of PsA treatment options, including anti-inflammatory drugs and anti-TNFα which are prescribed more frequently in men with PsA, while discrepancies have been reported in the prescription of DMARDs, especially MTX and sulfasalazine, in men and women. Furthermore, drug retention rates, which measure the overall benefit of a treatment (effectiveness) being the result of both positive (persistent efficacy) and

Figure 1. Flow chart for management of patients with suspected pancreatic injury

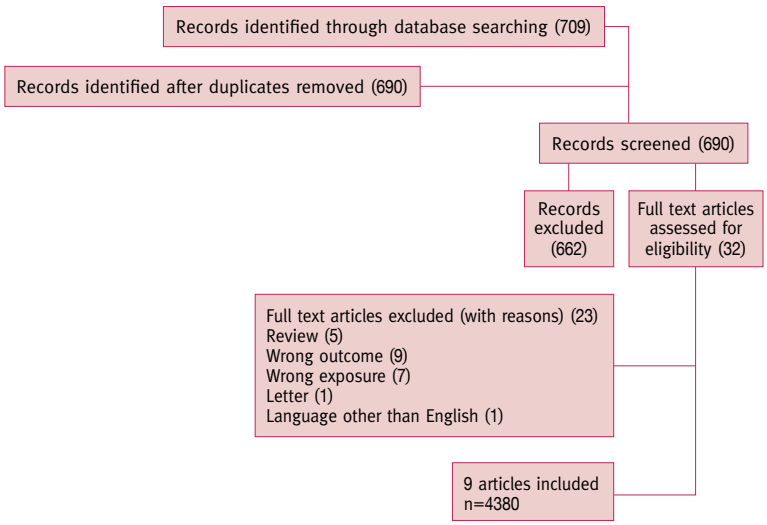

Table 1. Demographic characteristics of the population included in the studies

Study	Year	Geographic area	Total patients, n	Female, n (%)	Age, years	Disease duration, years
Fabbroni et al. [15]	2014	Italy	268*	126 (47)	Median 52 (IQR 44-61.5)	Mean 8.2 (7.2)
Fagerli et al. [16]	2014	Norway	440	204 (46.4)	Mean 46.5 (SD 11.6)	Median 5.2 (1.5-12.5)
Glintborg et al. [17]	2011	Denmark	764	396 (52)	Median 47 (IQR 38-56)	Median 5 (2-11)
Glintborg et al. [18]	2013	Denmark	1422	699 (49)	Median 48 (IQR 38-56)	Median 4 (1-10)
Gomez-Reino et al. [19]	2006	Spain	470	–	–	–
Heiberg et al. [20]	2008	Norway	172	63 (36.6)	Mean 45.7 (SD 10.8)	Mean 12.1 (SD 9.3)
Kristensen et al. [21]	2008	Sweden	261	128 (49)	Mean 47 (SD -)	–
Lie et al. [22]	2010	Norway	430	200 (46.5)	Mean 49.2 (SD 2.9)	Mean 4.4 (SD 6.6)
Mok et al. [23]	2014	Hong Kong	153	–	–	Mean 7.9 (SD 6.4)

*Including also patients with ankylosing spondylitis and axial spondyloarthritis

negative (loss of efficacy and adverse events) treatment effects, as well as a series of medical and non-medical factors (those not primarily related to the treatment effect) that influence drug use, are reported to be different between the sexes. These are generally longer in men [13], with women having better treatment response and a better prognosis, with lower rates of radiographic progression and lower values of the different scoring systems used in the evaluation of PsA and other SpA [14].

We performed a systematic literature review to investigate the role of sex in the use and retention rate of different conventional and biologic treatments in patients with PsA, and we propose our stance on this issue.

METHODS FOR THE SYSTEMATIC LITERATURE REVIEW

Our literature review was conducted to identify sex differences in drug retention rates in PsA patients treated with conventional DMARDs and biologic agents. The systematic review procedures we used conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Structured literature searches were conducted in June 2015 in the following databases: the Cochrane Library, PubMed/MEDLINE and EMBASE. Search terms included those for the disease, using the following medical subject headings (MeSH) and Emtree terms: psoriatic arthritis, treatment, and retention rate. Titles and abstracts were screened to determine if they met the inclusion criteria and, if potentially relevant, two independent reviewers selected relevant abstracts.

Included in the review were clinical trials, both interventional and observational, of patients with PsA.

Excluded were articles not concerning PsA, and reviews or editorials, in languages other than English, that involved children or animals. The selection process was performed by two authors, based on titles, abstracts and subsequently on full text papers. Figure 1 represents the flowchart of the selection process of this systematic literature review. Our outcome was drug retention rate. The full text analysis excluded 23 papers and the final analysis was performed on 9 full text papers.

With regard to data extraction, the year of publication, geographic area, study design and number of patients were recorded. Demographic data, such as sex, age and disease duration were also recorded. The outcome was defined by the presence of retention rates classified by sex. The quality of publications was determined by use of the Newcastle Ottawa Scale (NOS).

RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

A total of 709 articles were identified, of which 662 were excluded because they were not relevant, were duplicates, or used a language other than English. On reapplying the inclusion criteria, 32 articles were selected for full text analysis, resulting in 9 full text papers [15-23] for a total of 4380 patients. All articles were observational studies. The demographic features of subjects included in the studies are presented in Table 1.

The different treatments regarding retention rates and arthritis co-medications are listed in Table 2. The great majority of the included studies (8/9) investigated the retention rate of anti-TNFα agents (infliximab, adalimumab and etanercept), while only one study investigated MTX. The quality was assessed by the use of NOS, the grades ranged from * (1) to ***** (5) mean 4.2 (standard deviation SD ± 0.97).

Table 2. Treatments investigated and arthritis co-medications

Study	MTX n (%)	Treatment	Major observations
Fabbroni et al. [15]	44 (16.4)	IFX, ADA, ETN	Women have a shorter treatment duration, and a higher risk of treatment discontinuation
Fagerli et al. [16]	270 (61.3)	IFX, ADA, ETN	Women have a higher risk of treatment termination after 3 years, not statistically significant
Glintborg et al. [17]	410 (54)	IFX, ADA, ETN	Women have lower drug retention rates at 1 and 2 years; MTX does not affect drug survival
Glintborg et al. [18]	765 (53.8)	IFX, ADA, ETN	Women have lower drug survival after switching to the 2nd biologic agent
Gomez-Reino et al. [19]	–	IFX, ADA, ETN	Female sex is not associated with discontinuation
Heiberg et al. [20]	117 (68)	IFX, ADA, ETN	Women have a higher risk of discontinuation
Kristensen et al. [21]	161 (61.6)	IFX, ADA, ETN	No differences
Lie et al. [22]	430 (100)	MTX	No differences
Mok et al. [23]	–	IFX, ADA, ETN	Women have higher discontinuation rates

IFX = infliximab, ADA = adalimumab, ETN = etanercept, MTX = methotrexate

Fabbroni et al. [15] performed a retrospective and observational analysis of SpA patients treated with anti-TNF (213 diagnosed with PsA), for a total of 353 treatment courses of which 98 were interrupted, with no differences between the three biologic agents. Women manifested a shorter treatment duration compared to men, mean 20.1 months (SD ± 20.1) and 31.2 (SD ± 24.5) respectively. Women were also associated with a higher risk of treatment discontinuation, corresponding to an odds ratio (OR) of 2.227, 95% confidence interval (95%CI) 1.335–3.716.

Fagerli and colleagues [16] investigated the role of MTX co-medication in patients with PsA treated with anti-TNF. Female sex was identified as a predictor of treatment termination after 3 years in their cohort, but it did not reach statistical significance: hazard ratio (HR) 1.17, 95%CI 0.83–1.64.

Glintborg et al. [17] in 2011 reported the anti-TNF response and drug survival in 764 PsA patients derived from the DANBIO registry, for a total treatment period of 2135 person-years. In this cohort, 336 patients discontinued their treatment, mainly for lack of efficacy. The median drug survival was 2.9 years, with 1 and 2 year drug retention rates of 70 and 57% respectively. Sex differences were reported in retention rates for all the biologic agents included, with men manifesting a longer drug survival compared to women ($P > 0.001$). Interestingly, MTX use at baseline did not affect drug survival. In a subsequent analysis, female sex was confirmed to be associated with a shorter drug survival and was identified as a predictor (HR 1.8, 95%CI 1.3–1.9). The authors also reported other sex differences, both in baseline characteristics and clinical response. With regard to the former, women at baseline had significantly higher HAQ sores, Visual Analogue Scale (VAS) scores and tender joints, while manifesting lower scores for swollen joints. However, age, disease duration, DAS28 scores and baseline C-reactive protein (CRP) levels were not statistically different between sexes. Finally, men were associated with a better clinical response (OR 1.5, 95%CI 1.5–3.2). Furthermore, Glintborg et al. [18] in 2013 investigated whether sex influences drug survival after switching from the first to subsequent treatment lines. The results reported that men manifested a longer drug survival of the second biologic agent, compared to women ($P = 0.02$).

Gomez-Reino et al. [19] performed an observational study on more than 4000 patients with chronic arthritis from the BIOBADASER registry of Spain; 10% had a diagnosis of PsA. In the entire cohort investigated there were 5263 treatment courses and 1221 discontinuations. Even if the differences between the sexes in the subpopulations were not reported, the authors suggested that female sex is not an independent predictor of discontinuation (HR 1.25, 95%CI 1.10–1.43).

Heiberg and team [20] investigated the 1 year survival rates of three different anti-TNF biologic agents in rheumatoid arthritis (RA), PsA and SpA. The crude 1 year survival rate in PsA was 77.3%. Independently of the diagnosis, women were associated with a higher risk of treatment discontinuation (HR 1.51, 95%CI 1.19–1.93). Kristensen et al. [21] reported no differences between sexes in drug survival in PsA patients treated with anti-TNFα.

Only one study, by Lie et al. [22], reported the retention rate of MTX in PsA patients. MTX was discontinued in about 17% of the patients in the first 6 months of therapy, mainly for adverse events. Interestingly, no differences between sexes in the discontinuation rate of MTX were identified, as men were associated with an HR of 1.06 (95%CI 0.89–1.27). At 12 months 24% of PsA patients had discontinued MTX.

Mok and co-authors [23] compared the retention rates of different biologics used for the treatment of rheumatic diseases and found that women had an increased risk of anti-TNF discontinuation (HR 1.46, 95%CI 1.18–1.81).

THE CURRENT OUTLOOK

Gender medicine represents an avant garde branch of medicine, focusing on differences between women and men in health and disease. Semantics show that gender differs from sex, with the latter meaning the biology along with the anatomic

reproductive system and secondary sex characteristics, while gender refers more to the social side or personal identification, and may thus differ from the biology. In general terms and in the literature, however, these terms are used as synonyms and encompass genetics and environmental factors.

In autoimmune and rheumatic diseases, sex has historically been central, as most of these diseases more frequently affect women, with the most striking sex differences observed in Sjogren's syndrome, systemic lupus erythematosus, primary biliary cirrhosis, autoimmune thyroid disease and systemic sclerosis, with women representing over 80% of patients [24]. Sex is thus associated with the development of several autoimmune diseases, since hormonal factors and sex chromosomes have been identified as possible pathogenetic factors inducing a sexual dimorphism in the immune system [25].

Few studies have investigated the role of gender in PsA, and results are variable. Some studies report a male predominance of the disease [4], while others suggest a more equal distribution between sexes [3]. Clinical manifestations also differ between men and women, with male patients more frequently having axial or oligoarticular involvement. Conversely, women manifest polyarticular features more frequently, but reports are inconsistent since some studies did not find differences between different clinical subsets [26]. With regard to disease severity, in different studies men are reported to develop more erosions and in general a more aggressive radiographic progression [27]. A striking difference is reported in patient-reported outcomes and quality of life: women seem to be more disabled in daily activities and have higher disability scores [27], perhaps due to a different pain perception, which has been reported also in osteoarthritis. Fatigue seems also to be higher in women [7,27], who report a higher fatigue severity score [27]. These observations on quality of life and fatigue have been reported also for other rheumatologic conditions, especially RA and AS.

Co-morbidities are also an important issue in PsA and affect quality of life. Fibromyalgia is a major co-morbidity in PsA [28]. However, it may be difficult to assess the real disease activity in these patients due to a low correlation of joint count and biomarkers, i.e., CRP, and also because of the large overlap of enthesis and tender points [29].

As the clinical manifestations of PsA are variable, so are the treatment options different, ranging from traditional DMARDs for peripheral arthritis to biologics targeting TNFα or other pro-inflammatory cytokines for severe disease or disease with axial involvement. The use of traditional DMARDs is reported similarly in both sexes [30], with prescriptions more likely in women [27], even if we suggest that sexual factors, i.e., pregnancy, may affect the prescription of such drugs in young women. Biologics conversely seem to be more prescribed in men [30], perhaps due to higher axial involvement in males.

Retention rate is an indirect measurement of treatment efficacy and is currently used as an efficacy outcome in many studies. Our systematic review of the literature supports the view that women manifest a shorter treatment duration with anti-TNFα biologics compared to men [15,17,18,20]. Interestingly, only one study addressed the retention rate of MTX in PsA, reporting no differences between genders [22].

THOUGHTS FOR THE FUTURE

The PsA research agenda is moving fast to identify new biomarkers for disease early diagnosis, prognosis and stratification, and gender medicine seems to be a major crossroad towards personalized medicine, even though it is commonly overlooked. Genetics, which represents is a major risk factor for psoriasis and PsA, with the former being associated mainly with HLA-Cw*06 [31] and the second with HLA-B*27 [7], may provide further help in choosing the most appropriate therapy, as patients carrying the HLA- Cw*06 allele seem to respond better to ustekinumab [31]. Women may also benefit more from this treatment since they are reported to carry the HLA-Cw*06 allele more frequently; in contrast, HLA-B*27 is more frequent in men. Twin studies in the future may help to dissect the role of genetics in the development of PsA, and also help in the identification of environmental risk factors, such as smoking or trauma [32]. Moreover, PsA has been associated also with the presence of anti-carbamylated protein (anti-CarP) antibodies, found also in RA, suggesting an autoimmune background of the disease [33] and possibly the opportunity for a specific diagnostic test for the disease.

Cardiovascular disease is an issue of major interest in PsA and we expect that the research agenda will move forward in the following years, as occurred in rheumatoid arthritis. Indeed, patients with psoriasis and PsA have a higher incidence and prevalence of myocardial infarction and stroke compared to the general population [34]. This increased risk seems to be due not only to traditional risk factors but also to chronic systemic inflammation that may accelerate atherosclerosis [35]. Metabolic syndrome is also reported to be more frequent in PsA, thus increasing the cardiovascular risk burden and is associated with disease activity [35]. A screening tool has not yet been established and the existing ones may underestimate the real cardiovascular risk [36]; and since women and men have different risk profiles, gender should be taken into account when evaluating patients and choosing a therapy. We expect that in the future more targeted therapies will reduce this incremental burden of disease in PsA and thereby reduce morbidity and mortality of patients as well as the risk of paradoxical adverse events [37]. We suggest more accurate and closer monitoring in men and women after menopause [38].

Finally, microbiome analysis has become the most increasing area of interest in chronic inflammatory diseases. In the case of PsA, there is increased risk to develop Crohn disease and data on the intestinal microbiome show similar data for intestinal disease and psoriasis. However, few studies have

investigated skin and gut microbiome in patients with PsA or other SpA, with no focus on gender. Firmicutes, a major phylum of gut commensals, and especially the species *Faecalibacterium prausnitzii* and *Clostridium leptum*, are decreased in number, with a similar pattern seen in inflammatory bowel disease. These findings could establish a pathogenic link between gut inflammation and SpA. Moreover, the gut microbiome in PsA and psoriasis is decreased in number and diversity, similar to inflammatory bowel disease, as reported in a recent study [39]. These findings could help the future development of bacterial therapies that may replace the sick microbiome and reestablish a balance between microorganisms and the host, as observed in *C. difficile* infection. If the gut represents the ideal environment for microbiome development, the skin is less hospitable since microorganisms are more exposed to external agents and have fewer nutrients [40]. Some studies have investigated the composition of microbiome of the skin in psoriasis, showing the higher frequency of beta-hemolytic streptococcal infection and an abundance of *Propionibacterium* in psoriatic plaques. However, their interaction with the immune response is not yet clear, but a tolerance breakdown is suspected [40]. We expect that topical therapies will be developed in the next few years, as well as in other skin conditions, i.e., acne and rosacea.

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