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The Impact of Innovative Biologic Drugs in the Management of Psoriatic Patients

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Abstract

Purpose: Psoriasis is an immune-mediated dermatosis affecting 2% of the world population. Based on severity, different therapies are indicated: systemic drugs (cyclosporine (CsA) and methotrexate (Mtx)) are administered in severe cases; in patients that do not respond or do not tolerate these molecules, biologic drugs (Etanercept, Infliximab, Adalimumab, and Ustekinumab) are used as well. However, an appropriate management of patients still remains a critical goal still. This retrospective observational study investigated the effectiveness of systemic therapies in the treatment of severe psoriatic patients of the Local Health Authority (LHA) of Treviso, focusing on biologic *vs* synthetic drugs. *Methods:* The analysis was performed on the databases of territorial and hospital prescriptions, therapeutic plans, exemption code, blood laboratory tests and hospitalizations. *Results:* The analysis allowed the identification of a cohort of 871 psoriatic patients. Among them, articular, cardiovascular and immune-mediated complications are frequent comorbidities, sharing with psoriasis a similar genetic predisposition and inflammatory basis. In the LHA of Treviso, 11% of identified psoriatic patients were treated with biologics. Considering blood inflammatory parameters (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), the study revealed that the association of biologic and synthetic therapies (methotrexate) significantly reduces patient inflammatory state (mean CRP value <0.5 mg/100mL; mean ESR value<15mm/hour for men and <20mm/hour for women). *Conclusions:* The obtained results show clearly that innovative therapies represent a real contribution in the treatment of both psoriasis and its well-known comorbidities. An effective management will therefore require a systemic holistic approach, targeting the psoriatic pathology beyond skin.

Keywords

Severe Psoriasis, Immune-Mediated Comorbidities, Biologic Drugs, Inflammatory Parameters

1. Introduction

Psoriasis is a chronic immune-mediated dermatological disease affecting 2% of the world population, with spontaneous remission occurring in about one-third of cases. The mean age of onset is estimated at 33 years, with 75% of cases starting before the age of 46 [1]. Considering clinical manifestations, different types of psoriasis can be distinguished: plaque psoriasis is the most common form of the disease, accounting for the 90% of cases, and manifests as raised, red, itchy and painful patches covered with dead skin cells. Lesions can be localized or widespread across the body; considering the coverage, in particular, psoriasis can be classified into a mild form (involving less than 2% of the body surface, where 1% is represented by an hand palm), a moderate form (with 2–10% of the body surface involved), and a severe form (with more than 10% of the body surface involved) [2].

Based on the severity of the pathology, different therapies are indicated for the treatment of psoriatic lesions. According to established guidelines, phototherapy and topical treatments such as corticosteroids are common therapies in the management of mild and moderate psoriasis; in cases of

severe psoriasis, systemic therapies are administered as well. In the last case cyclosporine (CsA) and methotrexate (Mtx) are the first-line systemic drugs, given their immune-suppressive and anti-proliferative actions.

In patients with severe psoriasis that do not respond or do not tolerate these two molecules, innovative biologic drugs targeting the pro-inflammatory cytokines tumor necrosis factor-α (Etanercept, Infliximab and Adalimumab) and interleukin-12/23 (Ustekinumab) are used as well. Besides been approved in the treatment of severe psoriasis, Infliximab, Adalimumab and Ustekinumab are approved for the treatment also of PsA. Up to 30% of patients with psoriasis, in fact, develop also PsA which, in turn, is accompanied by cutaneous psoriasis in more than 90% of cases [3],[4].

In addition to PsA, severe psoriasis is reported to associate with cardiovascular complications and obesity. These share with psoriasis inflammatory mechanisms such as alterations in angiogenesis and Th-1-mediated inflammation [5]-[7]. This immune-activation further predisposes psoriatic patients to the development of other chronic autoimmune co-pathologies, such as Crohn's disease, chronic obstructive lung disease, and multiple sclerosis, leading to an aggravation of patient clinical condition and a reduction in quality of life and life expectancy [8].

The present retrospective observational study aimed to investigate the effectiveness of systemic synthetic vs. biologic therapies in the management of psoriasis in the Treviso LHA.

2. Methods

In the current retrospective observational study conducted in the LHA of Treviso, the following databanks were consulted for the years 2011-2013: territorial and hospital prescriptions (ATC codes: L04AD01 cyclosporine; L01BA01 methotrexate; L04AB01 Etanercept; L04AB02 Infliximab; L04AB04 Adalimumab; L04AC05 Ustekinumab), therapeutic plans, exemptions (exemption code 045 for the psoriatic pathology), blood laboratory tests (inflammatory parameters: CRP, and ESR), and schedules of hospital discharges (ICD-9 696.0 PsA, 696.1 other psoriasis, and 696.2 para-psoriasis). The linkage between the different databases allowed identification of the cohort of prevalent patients to the psoriatic pathology for the considered triennium; for these patients, the date of identified incidence and the exposition to therapies were investigated, as well. Based on such prescriptions, the psoriatic cohort was divided into mild-to-moderate (untreated or topically treated) and severe psoriatic patients (treated with CsA, Mtx and/or biologics). Considering all causes of hospitalizations that occurred in the triennium 2011-2013, comorbidities affecting psoriatic patients were investigated. In particular, the study focused on autoimmune comorbidities, consulting the databanks of exemptions and of hospital discharges: rheumatoid arthritis (ICD-9 714*, 7751; EC 006*), thyroiditis of Hashimoto (ICD-9 245*; EC 056*), type 1 diabetes (ICD-9 250*), multiple sclerosis (ICD-9 340; EC 046*), systemic erythematous lupus (ICD-9 37334, 6954, 7100; EC 028*), Crohn's disease (EC 009*), Basedow's disease (EC 035*), Sjogren's disease (ICD-9 7102, EC 030*), and ankylosing spondylitis (ICD-9 7200, EC 054*). Statistical analysis of data was elaborated using the Microsoft Access and Excel and STATA11, considering mean value, standard deviation, standard error of the mean and p value (statistical significance with $p<0.05$) and performing a t-Student test.

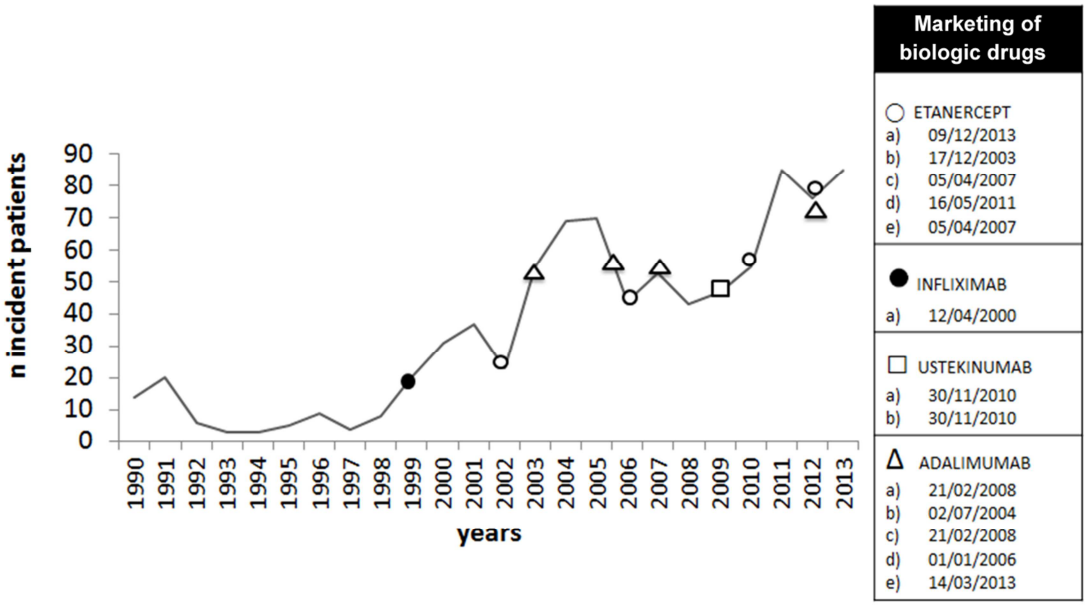

Fig. 1. *Incidence of psoriasis over years.*

The number of incident patients affected by psoriatic pathology (ordinate) reported as a function of each year (abscissa); the considered period ranges from 1990 to 2013. The graph shows also the dates of commercialization of new formulations of biologic drugs (● Infliximab; ○ Etanercept; Δ Adalimumab; □Ustekinumab).

3. Results

3.1. Identification and Characterization of the Psoriatic Population

In the LHA of Treviso, the cohort of prevalent psoriatic patients for the triennium 2011-2013 was composed of 871 patients (0.2% of the population), among which 485 were men. The mean age of identified onset of the disease was 55 years. Considering the year of incidence of prevalent psoriatic patients, an exponential increase in the tendency line can be noted over time, ranging from 14 incident patients in 1990 to 85 incident patients in 2013. In particular, a massive increase was noted in correspondence to the years of commercialization of innovative anti-psoriatic biologic therapies [Fig. 1].

3.2. Systemic Anti-Psoriatic Treatments Administered

Considering pharmaceutical prescriptions, 299 patients out of the 871 psoriatic patients were treated with CsA, Mtx and/or biologics and are therefore considered as affected by a severe form of the pathology (0.07% of the total population and 34% of the psoriatic population). During the triennium 2011-2103, the number of psoriatic patients treated with these systemic therapies significantly increased (209 in 2011; 218 in 2012; 249 in 2013).

Of the 299 severe-psoriatic patients, 96 were treated with biologic drugs in mono- or co-therapy. Etanercept and Adalimumab were the most frequently used, with 33 to 42 patients treated each year with Etanercept, and 19 to 31 patients treated with Adalimumab (2011-2013, respectively); Infliximab and Ustekinumab were used instead by less than 10 psoriatic patients per year.

3.3. Comorbidities Affecting Psoriatic Patients

Considering hospitalizations directly related with psoriasis, 141 patients were hospitalized in the triennium 2011-2013, i.e. 16% of the psoriatic population. Furthermore, 41% and 35% of the mild-to-moderate and of severe psoriatic patients, respectively, underwent hospitalizations for whichever disease: the main comorbidities, in particular, were articular, cardiovascular, and cancer.

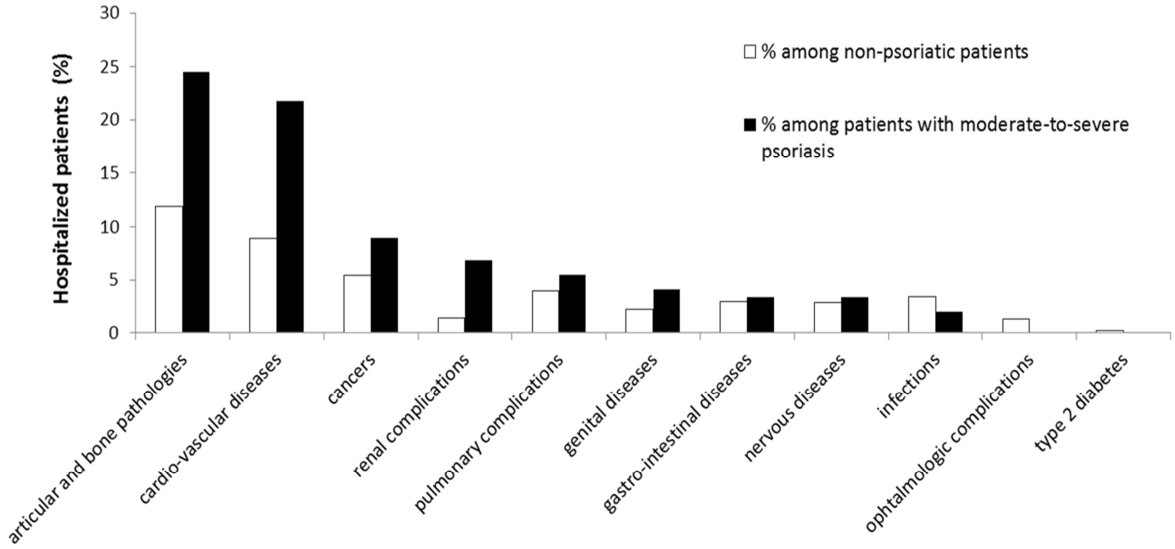

Fig. 2. *Hospitalizations of patients treated with cyclosporine or methotrexate and/or biologics.*

Treated patients were divided into two cohorts: those treated for psoriasis (black histograms) and those treated with these drugs for other therapeutic indications (white histograms). The percentage of hospitalized patients (ordinate) was calculated for both groups, considering only hospitalizations occurring between 2011 and 2013 and after beginning systemic treatment. The pathological macro-areas related to the causes of hospitalization are reported in abscissa.

Comparing hospitalizations of severe psoriatic patients with those of non-psoriatic patients treated with CsA, Mtx and/or biologics for other indications, the percentage of hospitalized psoriatic patients was significantly higher among the psoriatic cohort [Fig. 2]. The profile of the two cohorts in terms of gender and age were comparable. In particular, articular and bone diseases were two-fold more frequent among psoriatics compared to the second group of patients (24.5% and 9.2% of patients hospitalized, respectively). Similarly, the percentage of hospitalized psoriatic patients was considerably higher (ratio between the two percentages > 1,5) also considering cardiovascular diseases, cancers, renal complications, genital diseases and infections. The incidence of immune-mediated diseases in the psoriatic population was then compared to that in the total population of the Treviso LHA (416.000 people) [Fig. 3]. The profile of the two cohorts in terms of gender and age were comparable. The obtained results showed autoimmune pathologies to be significantly more frequent within the cohort of psoriatic patients; in particular, the incidence of rheumatoid arthritis was 20 times higher among

psoriatic patients compared to the total population (10% and 0.5% of affected patients, respectively). Similarly, ankylosing spondylitis and type 1 diabetes were 7 and 5.5 times more frequent, respectively, among psoriatic patients compared to the total population. The incidence of Sjogren's disease, systemic lupus erythematosus and Crohn's disease among psoriatic patients resulted considerably higher, as well. Smaller or no difference, instead, was reported for Hashimoto's thyroiditis, Basedow's disease and multiple sclerosis.

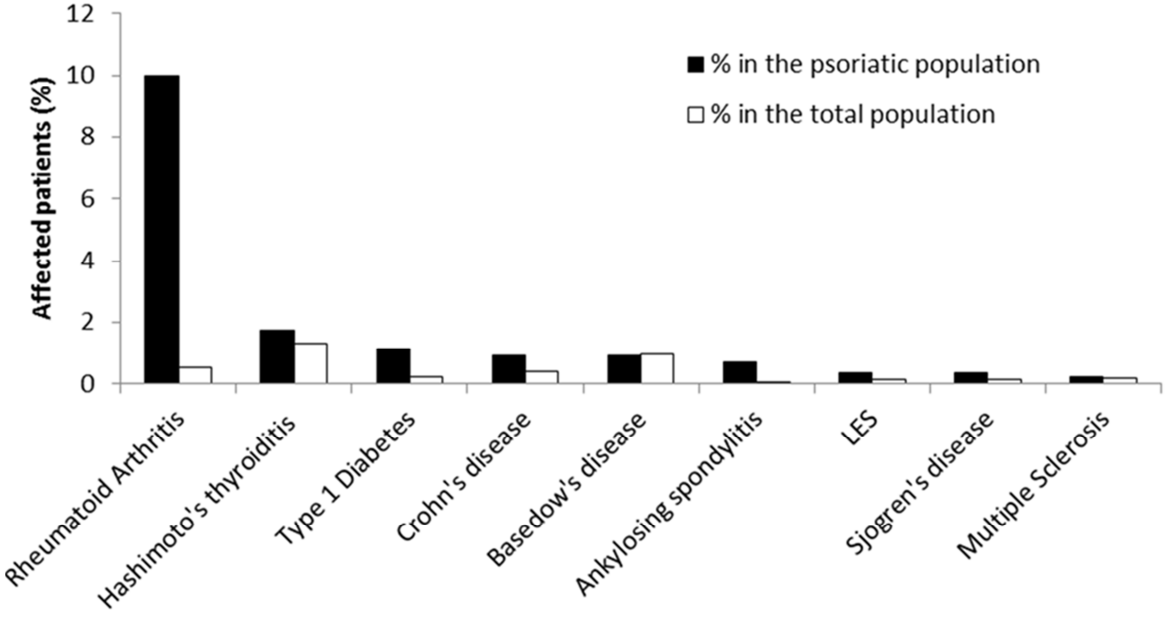

Fig. 3. *Autoimmune comorbidities affecting psoriatic patients.*

Percentage of patients affected by autoimmune pathologies other than psoriasis based on hospitalizations DIA0 and on exemption codes. The percentage of psoriatic patients affected by autoimmune comorbidities has been compared to the percentage of affected patients in the total population of the ULSS9 of Treviso.

3.4. Analysis of Blood Inflammatory Parameters

As inflammation is a key condition sustaining both psoriasis and its comorbidities, blood values of the inflammatory parameters CRP and ESR were analyzed before and during the period of therapeutic treatment (monotherapy with synthetic drugs-CsA or Mtx; monotherapy with biologics; cotherapy Mtx+ biologic drug) [Table 1]. The mean lifespan of therapeutic treatment calculated for patients that are incident to the considered treatment in the triennium 2011-2013, in particular, was 14 months for CsA and Mtx, 15 months for monotherapy with biologics, and 9 months for the co-therapy Mtx + biologics.

Table 1. *Blood levels of inflammatory parameters in psoriatic patients divided according to therapeutic treatment.*

	CRP (male + female patients)			**ESR (female patients)**			**ESR (male patients)**		
Threshold level	**0,5 mg/100ml**			**20 mm/hour**			**15 mm/hour**		
	CsA-Mtx	**Biologics**	**Co-therapy**	**CsA-Mtx**	**Biologics**	**Co-therapy**	**CsA-Mtx**	**Biologics**	**Co-therapy**
Before whichever therapy	1,32 ± 0,2 mg/100ml* (n=101)			29 ± 3 mm/hour* (n=48)			21 ± 2 mm/hour* (n=54)		
Before considered therapy	1,61 ± 0,4 mg/100ml* (n=64)	0,86 ± 0,3 mg/100ml (n=25)	0,63 ± 0,2 mg/100ml (n=13)	32 ± 4 mm/hour* (n=29)	29 ± 5 mm/hour (n=13)	21 ± 5 mm/hour (n=6)	22 ± 2 mm/hour* (n=34)	18 ± 2 mm/hour (n=13)	22 ± 5 mm/hour (n=8)
During therapy	0,86 ± 0,1 mg/100ml*$_s$ (n=149)	0,69 ± 0,2 mg/100ml (n=38)	0,16 ± 0,05 mg/100ml* (n=13)	31 ± 2 mm/hour* (n=71)	28 ± 4 mm/hour (n=21)	16 ± 3 mm/hour (n=7)	23 ± 1 mm/hour* (n=73)	19 ± 2 mm/hour (n=21)	11 ± 1 mm/hour* (n=8)

Mean values of C-reactive protein (CRP) ± standard error and Erythrocyte Sedimentation Rate (ESR) ± standard error analyzed before the beginning of whichever treatment, in order to identify the basal inflammatory level of severe psoriatic patients. Furthermore, patients have been divided into CsA or Mtx-treated, Biologics-treated and those treated in cotherapy with biologics + Mtx (columns "CsA-Mtx; Biologics; Co-therapy); patients switching from one group to another in the period of observation have been considered in both groups. For each of these groups, the mean values of CRP and ESR were analyzed before and during the period of treatment + 60 days. The threshold level of CRP is 0.5 mg/100ml; the threshold levels of ESR are 20 mm/hour for women and 15 mm/hour for men. Significance vs threshold level: *p<0.05. Significance both vs threshold level and vs during therapy: *s p<0.05. The number of observations is reported in brackets.

Considering CRP blood tests, the basal mean value for the whole psoriatic population before treatment was 1.32 mg/100ml (95% CI 0.83 - 1.81), i.e. significantly above the threshold level of 0.5mg/100ml ($p<0.01$). Considering the different therapeutic groups, the mean value for patients in monotherapy with CsA or Mtx was 1.61 mg/100ml (95% CI 0.89 - 2.34) before treatment and 0.86 mg/100ml (95% CI 0.57 - 1.15) in the period of treatment, i.e. both CRP values were significantly above the threshold level ($p<0.01$ and $p<0.05$, respectively). For patients in monotherapy with biologics, instead, the mean CRP value was 0.86 mg/100ml (95% CI 0.23 - 1.48) before treatment and 0.69 mg/100ml (95% CI 0.25 - 1.13) in the period of treatment; both mean values, although not significantly different were above the threshold level ($p>0.05$). For patients treated in co-therapy, instead, the mean value before therapy start was 0.63 mg/100ml (95% CI 0.10 - 1.17), i.e. above the threshold level ($p>0.05$); on the other hand, this level significantly decreases under the threshold level in the period of therapeutic treatment, being 0.16 mg/100ml (95% CI 0.05 - 0.27; $p<0.001$).

Focusing on ESR blood tests instead, female and male patients were analyzed separately. For female patients, the basal level of ESR for the whole psoriatic population before treatment was 29 mm/hour (95% CI 23.09 - 35.33), i.e. significantly higher than the threshold level of 20 mm/hour ($p<0.01$). Considering the different therapeutic groups, the mean values of ESR for patients in monotherapy with synthetic drugs were 32 mm/hour (95% CI 23.27 - 41.09) and 31 mm/hour (95% CI 26.70 – 35.90) before and during therapeutic treatment, respectively, being significantly higher than the threshold level ($p<0.01$ and $p<0.001$, respectively). Similarly, for male patients, mean basal values for the whole psoriatic population before treatment was 21 mm/hour (95% CI 17.24 - 24.47), i.e. significantly above the threshold level of 15 mm/hour ($p<0.01$). Considering again the different therapeutic groups, mean values for patients in monotherapy with CsA or Mtx were above the threshold level both before and during treatment, being 22 mm/hour (95% CI 17.05 – 26.79) and 23 mm/hour (95% CI 17.05 – 26.79), respectively ($p<0.01$ and $p<0.00$, respectively).

Considering patients in monotherapy with biologics drugs, mean values of ESR for female patients were 29 mm/hour (95% CI 18.04 - 40.25) and 28 mm/hour (95% CI 19.52 – 36.86) before and during therapeutic treatment: both were above the threshold level, although failed to achieve statistical significance ($p>0.05$). Similarly, male patients treated with biologics in monotherapy presented mean values of ESR higher than the threshold level, being of 18 mm/hour (95% CI 12.79 - 23.61) and 19 mm/hour (95% CI 13.46 – 23.88) before and during the therapeutic treatment, respectively, although these values failed to achieve statistical significance ($p>0.05$).

For patients in co-therapy instead, the mean value before beginning co-treatment was 21 mm/hour (95% CI 8.81 – 33.66) for female patients and 22 mm/hour (95% CI 8.88 – 34.82) for male patients: These values were higher than the threshold level for both genders, although failed to achieve statistical significance ($p>0.05$). Levels appeared to decrease considerably under the threshold level during therapeutic treatment, being 16 mm/hour (95% CI 9.07-22.65) for women and 11 mm/hour (95% CI 8.35 – 14.63) for men ($p>0.05$ and $p<0.05$, respectively).

4. Discussion

Psoriasis is a chronic immune-mediated cutaneous disease characterized by a massive epidermal hyperproliferation and that manifests as erythematous plaques with large scaling [9]. Progression of the disorder leads to both physical and psychological complications that deeply affect the patient's quality of life [8], [10]-[12]. In spite of this, very little is known about the epidemiology of psoriasis. The present retrospective observational study investigated the incidence and overall burden related to psoriasis in the LHA of Treviso. According to this analysis 0.2% of the resident population was clearly identified as affected by psoriasis (871 out of 416,000 persons); this percentage is much lower compared to the national prevalence of 2.9 % reported by Saraceno et al.[13]. It should be noted, however, that data extrapolated in the present study only allowed the identification of striking manifestations of the psoriatic pathology (such as hospitalization, an exemption or administration of biologic therapies), thereby preventing the detection of milder manifestations that probably involve the majority of psoriatic patients.

The predominant identification of severe cases is further highlighted by the male prevalence found in this analysis (56% of psoriatic patients within the detected cohort were men, whereas in the overall population of the LHA, 51.30% of the residents were women). According to literature, psoriasis affects both genders equally [14], but a male prevalence has been noted in its most severe forms and in PsA [15; 16]. Similarly, the older age of identified onset (55 years), compared to that of 33 years reported in [1], further indicates that the identified date of incidence is not that of the first clinical manifestation, but rather that of a later worsening of the pathology.

Evaluating the incidence date in relation to the pathology of prevalent psoriatic patients, a clear increase in the incidence trend can be detected over time. Considering that episodes of remission are quite rare, especially in the severe forms, these data appear to confirm an increasing trend that has actually characterized the epidemiology of psoriasis. According to literature, an increasing incidence has been reported in both pediatric and adult psoriasis [17],[18]; explanations may lie in both a concomitant real increase in environmental and psycho-physical risk factors, as well as an improvement of databanks and of diagnostic methods (therapeutic plans). The present analysis further suggests that the marketing and availability of innovative biologic therapies could have been a factor in encouraging a clear identification and recognition of the pathology, in order to have access to such promising treatments.

Actually, 11% of the psoriatic patients examined by this study were being treated with biologic therapies (34% of the cohort of severe psoriatics). This percentage of biologic-treated patients is included in the 34% of patients detected as systemically treated (i.e. treated with CsA, Mtx and/or biologics) and that were classified as affected by a severe form of the pathology. The remaining 66% of patients were untreated or only topically treated and should therefore be considered as affected by a mild or moderate form of the pathology. It is worth noting, however, that although these patients are untreated or only mildly treated, they all have an exemption and/or underwent hospitalizations connected with psoriasis. These data confirm what Lebwohl et al. reported in a recent study [19], in which more than 80% of North American and European patients with moderate or severe forms of psoriasis received no treatment or topical treatment only.

An appropriate management of psoriasis remains to be firmly established, and the stabilization of patient clinical condition is still very critical. In particular, as this present study reveals, hospitalizations directly related to psoriasis involved 16% of the psoriatic population of the LHA of Treviso (141 out of 871 patients), with 50 to 60 psoriatic patients hospitalized per year (2011-2013), which represents a clear economic, social and psycho-physical burden.

Besides hospitalizations directly related to psoriasis, the present analysis indicates that also hospitalizations related to comorbidities involved a consistent percentage of psoriatic patients (41% and 35% of patients non-systemically and systemically treated, respectively). In particular, the main causes resulting from hospital discharges were articular complications and cardiovascular comorbidities. The remarkable incidence of articular disorders is likely connected to PsA, an inflammatory arthropathic comorbidity affecting up to 30% of psoriatic patients [3]; similarly, cardiovascular diseases have been associated with psoriasis since 1978 [20], with its chronic inflammatory status representing a considerable risk factor for myocardial infarction and atherosclerosis [8], [21]-[23]. Beside this intrinsic predisposition, cardiovascular complications following administration of common anti-psoriatic drugs such as CsA should be taken into account as well [8].

For this reason, the present analysis investigated whether a link between therapies (CsA, Mtx and biologics) and comorbidities existed, by comparing pathologies affecting psoriatic and non-psoriatic treated patients. Our results, however, failed to support such a correlation: comorbidities in general were significantly more frequent within the psoriatic population, therefore suggesting that psoriasis per se represents a predisposing condition. As Boehncke and Sterry stated [8], psoriasis appears more and more as "a systemic inflammatory disorder" whose manifestations and implications go far beyond its dermatological consequences. Such inflammation and abnormal immune-activation is evident also in all autoimmune diseases affecting a significant percentage of psoriatic patients. The current study, in fact, highlighted that autoimmune disorders (rheumatoid arthritis, thyroiditis of Hashimoto, type 1 diabetes, multiple sclerosis, systemic erythematous lupus, Crohn's disease, Basedow's disease, Sjogren's disease, and ankylosing spondylitis) present an extremely high incidence within the psoriatic population; rheumatoid arthritis in particular appears to be 20 times more frequent among psoriatic patients compared to the total population of the LHA of Treviso. However, these data appear overestimated: according to the literature, the odds ratio of developing rheumatoid arthritis is 3.6 for psoriatic patients compared to the general population [24], i.e. a predisposition in terms of improper immune-activation exists but the incidence of this comorbidity is much smaller than that observed in the present study. A rheumatic complication in the selected psoriatic population is therefore much more likely to be connected to PsA, a comorbidity affecting a massive percentage of the psoriatic population [3]. Hospitalizations affecting these patients could therefore be related to such a generalized articular complication rather than to rheumatoid arthritis per se.

The correlation of psoriasis with other immune-mediated diseases is well-established, since a common genetic predisposition and cytokine profile has been demonstrated [25]-[27]. In light of this, tumor necrosis factor-α as well as interleukin-12 and interleukin-23 have been exploited as promising targets of new biologic immune-regulating therapies, providing a bilateral contribution to the management of the overall inflammatory state of psoriatic patients.

In the present study, blood laboratory tests of CRP and ESR were investigated in order to evaluate the effectiveness of systemic anti-psoriatic therapies in reducing inflammation. The results confirm an evident inflammatory condition, with CRP and ESR being significantly altered in psoriatic patients before treatment. Analyzing these parameters following therapy with CsA or Mtx, a general decrease was noted, although their therapeutic target(s) could be be ascertained. Furthermore, the inflammatory values obtained with a CsA-Mtx treatment were comparable to those observed in patients before a biologic therapy: these patients, in fact, presented lower inflammatory levels compared to basal of the whole population, probably reflecting the benefits of the synthetic therapies previously administered according to established guidelines. These values, however, were considerably higher than the threshold level, indicating inefficacy of CsA and Mtx in reducing the overall inflammatory condition. Similarly, administration of biologic drugs in monotherapy appeared to further decrease both CRP and ESR levels, but the hematic inflammatory target was probably not reached effectively, since the mean values detected during the treatment period were significantly above the threshold level. On the other hand, the association of these two types of treatment (Mtx + biologics) significantly decreased the levels of the analyzed parameters to the allowed range, thereby effectively counteracting the inflammatory status of psoriatic patients.

The results of the present study confirm a recent review by Busard et al. [28] indicating the co-therapy Etanercept +Mtx to be more effective than a biological monotherapy in improving psoriatic lesions. Similarly, co-administration of Mtx is recommended for Infliximab-treated patients, in order

to avoid the formation of antibodies against the murine part of the chimeric antibody.

5. Conclusion

New biologic drugs can be seen as a valid contribution to classic synthetic therapies in reducing the extended inflammatory condition sustaining both psoriasis and its well-known comorbidities; further analysis on a wider population will allow for a better investigation of the true potential of such innovative therapies. Only an effective and in-time therapy able to counteract psoriasis on multiple fronts, combined with an early diagnosis, will lead to a real improvement of a disease that continues to profoundly compromise patient quality of life.

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