The typical cutaneous manifestations and chronic course of psoriasis have a significant impact on patients’ quality of life as psoriasis is associated with potentially invalidating psychological and social consequences (6). Moreover, in patients with severe disease there is a higher mortality risk compared to the general population (hazard ratio [HR] 1.5; 95% confidence interval [CI] 1.3-1.7) (7,8).

With a prevalence of 2.9-3.1% (7,9) and an incidence of 230-310 new cases per 100,000 persons/year (10), psoriasis is one of the most common dermatological diseases with about 1.5-2.5 million patients in Italy. The diagnosis of psoriasis is usually clinical and based mainly on the physical examination and the patient’s medical history; skin biopsy is rarely needed to confirm the diagnosis (11).

There are several forms of psoriasis, although plaque psoriasis (PP) is the most common (about 80% of patients) (11-13). PP is characterized by the presence of erythematous-desquamative lesions with clear margins, mainly located on the limbs (knees and elbows), lumbosacral region and scalp (11,12), often accompanied by symptoms such as itching and pain (13,14). About 20% of patients develop moderate-to-severe PP (15,16).
Different outcome measures are used to evaluate the severity of PP and the efficacy of treatment; the Psoriasis Area and Severity Index (PASI) is one of the most frequently used (16-18). PASI combines a quantitative (proportion of affected area for each body region) and a qualitative (presence of erythema, scaling and skin thickening) skin disease assessment.

The PASI score is measured on a scale from 0 (absence of disease) to a maximum of 72 and response to treatment is often measured in terms of percentage decrease in the PASI score, with values of 75% (PASI75), 90% (PASI90) and 100% (PASI100) usually reported in clinical trials (15,16). A PASI score >10 generally indicates moderate disease (15,16).

At present, there is no cure for PP, while several treatments can, however, provide control of symptoms of the disease.

Compared to the administration of traditional systemic therapies, the availability of new biological agents (anti-tumor necrosis factor [TNF]-α and interleukin [IL] inhibitors) has profoundly changed the management of moderate-to-severe PP (19). In particular, the use of IL inhibitors such as ustekinumab (IL-12/23), secukinumab (IL-17), guselkumab (IL-23), tildrakizumab (IL-23) and risankizumab (IL-23) allows a substantial proportion of patients to achieve significant levels of skin clearance (19).

Objectives

The present analysis was carried out to estimate the number needed to treat (NNT) of the IL inhibitors currently reimbursed in Italy for the treatment of moderate-to-severe PP: brodalumab, guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab and ustekinumab.

Methods

Network meta-analysis

This analysis is based on the results of a recent network meta-analysis (NMA) by the Cochrane Database of Systematic Reviews (19). NMA is a technique that synthesizes direct and indirect comparisons of interventions (i.e. drugs). The Cochrane NMA compared efficacy and safety of the principal drugs (conventional systemic therapies, small molecules, anti-TNF-α, IL inhibitors) used for the treatment of moderate-to-severe PP (19). Drugs were compared and ranked according to effectiveness considering the PASI90 score (20,21).

The NMA considered a total of 140 randomized controlled trials (RCTs), involving 51,749 patients (overall average age: 45 years; male: 67%). Eighty-two trials compared systemic treatments with placebo, 41 trials compared systemic treatments with systemic treatments and 17 trials compared systemic treatments with systemic treatments and placebo. Most RCTs were short term and the PASI90 scores presented in the NMA were measured from 8 to 24 weeks after patients were randomized (induction phase). In terms of reaching PASI90, anti-IL-17 (ixekizumab, secukinumab and brodalumab), anti-IL-12/23 (ustekinumab), anti-IL-23 (risankizumab, guselkumab and tildrakizumab) and anti-TNF-α were significantly more effective than small molecules and conventional systemic therapies (19). At drug level, ixekizumab, secukinumab, brodalumab, risankizumab and guselkumab were significantly more effective (PASI90) than ustekinumab, adalimumab, certolizumab and etanercept (19). For the risk of serious side effects, there were no significant differences between any of the systemic treatments compared with placebo (19).

Table I lists the IL inhibitors that are currently reimbursed by the Italian National Health Service (INHS) with their relative efficacy (PASI90) compared to placebo (19). The NMA results showed that ixekizumab was more effective than other ILs in treating moderate-to-severe PP when assessed using an outcome that required 90% improvement (PASI90).

**Number needed to treat**

The concept of NNT was presented by Laupacis et al in 1988 (22). The NNT is an absolute effect measure which represents the number of patients to be treated to obtain a therapeutic benefit (responders) (22-24). The NNT corresponds to the reciprocal of the absolute risk reduction (ARR), where the ARR corresponds to the difference in the incidence of the event between the experimental (experimental event rate, EER) and control groups (control event rate, CER) (22-24), as shown in Equation [1]. In the present analysis the NNT was calculated considering the efficacy (PASI90) compared to placebo for the IL inhibitors reimbursed in Italy for the treatment of moderate-to-severe PP. In general, the NNT is the number of patients that need to be treated with one of the IL inhibitors (experimental group) compared to placebo (control group) to significantly reduce the disease activity by 90%.

**Table I - Network meta-analysis: PASI90 induction phase results**

| Drug            | No of participants (studies) | Treatment (95% CI) | Placebo |
|-----------------|------------------------------|--------------------|---------|
| Brodalumab      | 4,109 (5 RCTs)               | 32.9% (27.3%-39.8%)| 1.5%    |
| Guselkumab      | 1,767 (5 RCTs)               | 38.8% (31.3%-47.9%)| 1.5%    |
| Ixekizumab      | 3,268 (4 RCTs)               | 42.2% (34.8%-51.2%) | 1.5%    |
| Risankizumab    | 1,476 (4 RCTs)               | 41.5% (34.3%-50.2%) | 1.5%    |
| Secukinumab     | 2,895 (8 RCTs)               | 36.0% (30.0%-43.1%) | 1.5%    |
| Tildrakizumab   | 1,903 (3 RCTs)               | 25.6% (19.4%-33.8%) | 1.5%    |
| Ustekinumab     | 4,231 (9 RCTs)               | 25.8% (21.7%-30.6%) | 1.5%    |

CI = confidence interval; PASI = Psoriasis Area and Severity Index; RCT = randomized controlled trial.

*PASI90 scores presented in the NMA were measured from 8 to 24 weeks after patients were randomized (induction phase).
obtain a therapeutic benefit (achieve PASI90). It is useful to remember that the lower the NNT, the higher the effectiveness of the intervention versus the selected comparators.

\[
\text{NNT} = \frac{1}{\text{ARR}} = \frac{1}{(\text{ERR} - \text{CRR})} = \frac{1}{(\text{PASO}_90 - \text{PASO}_90')}
\]

where IL = IL inhibitor; P = placebo.

**Sensitivity analysis**

A sensitivity analysis was performed with the aim of evaluating the degree of uncertainty of the basecase NNT results (25). As the efficacy data (PASI90) estimated by the NMA (19) was used to calculate the NNT values, the uncertainty of the basecase NNT values was tested in a one-way sensitivity analysis (OWSA) according to the confidence interval efficacy data (PASI90) of each IL reported in the NMA (Tab. I). This analysis was performed to determine the impact of the efficacy data variation of the NNT values estimated in the base case.

**Results**

**Number needed to treat**

Referring to the PASI90 score, Figure 1 shows the NNT of the seven IL inhibitors in the induction phase of treatment. Considering the proportion of patients who achieve PASI90, ixekizumab always had the lowest NNT among all comparators.

**Sensitivity analysis**

Figure 1 details the results of the sensitivity analysis where the efficacy data (PASI90) are reported in the NMA (19) range according to the confidence intervals (Tab. I). In all comparisons (upper and lower bounds), ixekizumab remained the therapeutic alternative with the lowest NNT values.

**Discussion**

The Consolidated Standards of Reporting Trials (CONSORT) recommends the use of relative (i.e. relative risk) and absolute (i.e. NNT) measures of effect for RCTs (25, 26). Likewise, the British Medical Journal (BMJ) also requests to report relative and absolute risks in RCTs (23). However, the RCT results are not commonly reported in terms of NNT, while relative measures, such as relative risk or odds ratio, are more extensively used in scientific publications (27-30). Together with all the other measures of effects, the NNT should be a valuable supportive tool to assist physicians in selecting treatments in daily clinical practice (31, 32). Furthermore, the NNT should be used in benefit-risk assessments, thereby supporting health decision makers (33-35).

This study evaluated the NNT for the induction phase of seven IL inhibitors currently reimbursed by the INHS for the treatment of moderate-to-severe PP. Ixekizumab was associated with the lowest NNT compared to all other IL inhibitors. Our comparison is derived from the results of a Cochrane NMA (19) that highlighted the greater efficacy (PASI90) of ixekizumab compared to brodalumab, guselku-mab, risankizumab, secukinumab, tildrakizumab and ustekiu-numab in the treatment of moderate-to-severe PP. NMA, as indirect comparison, provides observational evidence, since the treatments being compared have not been randomized across studies. Compared to previous review, the Cochrane NMA included more treatment, more trials (n = 140) and more patients (n = 51,749). In the Cochrane NMA there is no evidence of heterogeneity either in direct comparisons or in the entire networks and there is no evidence that relevant

![Fig. 1 - NNT in the induction phase of treatment.*](image)

*PASI90 scores presented in the NMA were measured from 8 to 24 weeks after patients were randomized (induction phase).
variables such as age, sex, duration or severity of PP varied across comparison. We cannot assume that the clinical results are perfectly generalizable to the Italian context, but, anyway, we believe that the NMA is a valid statistical approach to generate comparative efficacy data (anti-IL vs placebo) when head-to-head comparisons are not available for all or the most of the treatments evaluated (36,37). Nevertheless, the lack of head-to-head comparisons could be a limitation of this analysis. To justify this lack of data, a sensitivity analysis on NMA PASI90 was conducted. The results of the sensitivity analysis confirmed the base case scenario.

Based on the results of another NMA (38), a Spanish study evaluated the NNT of ixekizumab, secukinumab, ustekinumab, adalimumab, etanercept and infliximab for moderate-to-severe PP (39). This NMA provided indirect comparisons (PASI75, PASI90 and PASI100) for all biologic drugs administered in the treatment of moderate-to-severe PP. Consistent with our finding, ixekizumab showed the lowest NNT for all PASI response scores.

Conclusions

Based on NMA's efficacy data (PASI90), ixekizumab showed the lowest NNT value for the treatment of moderate-to-severe PP compared to brodalumab, guselkumab, risankizumab, secukinumab, tildrakizumab and ustekinumab. The NNT allows to rank alternative treatments based on their efficacy, supporting clinicians, payers and other healthcare stakeholders on drug choice.

Authors’ contributions

RR designed the study and drafted the manuscript. AC, AM and SL reviewed the manuscript. All authors read and approved the final version of the manuscript.

Disclosures

Conflicts of interest: The agreement signed by Health Publishing & Services and Eli Lilly Italia S.p.A. does not create any entitship, joint venture or any similar relationship between parties. Health Publishing & Services is an independent company. Neither Health Publishing & Services nor any of their representatives are employees of Eli Lilly Italia S.p.A. for any purpose. RR is a consultant of Health Publishing & Services. AC has received honoraria as advisor or speaker from Abbvie, Janssen, Pfizer, Boehringer, Eli Lilly, Celgene, UCB, Galderma and Novartis. SA, AM and SL are full-time employees of Eli Lilly Italia S.p.A. Financial support: This research was made possible by an educational grant from Eli Lilly Italia S.p.A.

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