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Abbreviations used in this issue:

bid = twice daily
MM = multiple imputation
OR = odds ratio
PASI = Psoriasis Area and Severity Index
RCT = randomised-controlled trial
TNF-α = tumour necrosis factor alpha

Welcome to Issue 35 of Psoriasis Research Review.

First up we review a study showing surprisingly impressive results of etanercept in paediatric patients with plaque psoriasis. Following on, we investigate long-term drug survival in psoriasis patients receiving biologics in Hungary and discover that ustekinumab has the highest persistence rate at 3 years. Among the other studies included in this issue we look at biologic treatments for elderly patients, monthly vitamin D supplementation in mild psoriasis, the risk of malignancy with systemic psoriasis treatment, serious infections after systemically treated psoriasis, and switching of biologics in psoriasis and secukinumab in moderate-to-severe psoriasis.

We hope you find the latest issue of Psoriasis Research Review stimulating reading and look forward to any feedback.

Kind Regards,
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Effectiveness of etanercept in children with plaque psoriasis in real practice: a one-year multicenter retrospective study

Authors: Di Lernia V et al.

Summary: This retrospective analysis of data from centres in the ‘Pediatric Dermatology Group’ of the Italian Society of Dermatology studied the use of etanercept in 23 children and adolescents with moderate-to-severe plaque psoriasis. After 12 weeks, 56.5% of patients achieved ≥75% PASI improvement and 86.9% achieved a ≥50% improvement in PASI. This level of efficacy was sustained through 52 weeks; 15 patients were still receiving etanercept at the time of data collection. Therapy was suspended due to inefficacy in three patients.

Comment: Regular readers of Psoriasis Research Review will realise that I am partial to studies on paediatrics. I first wish to discuss an Italian study regarding etanercept in children with plaque psoriasis. It is a short 1-year multicentre retrospective study for which only 23 children were identified. This study was using a drug that most of us don’t use anymore because of its inferior potency compared to the newer agents. However, in this group, etanercept did give impressive results at week 12; 56.5% had PASI 75, 86.9% PASI 50. Three of the 23 didn’t respond and 15 out of 23 were still on the drug at week 52.

Reference: J Dermatolog Treat. 2017;28(7):635-41
Abstract

Long-term drug survival and predictor analysis of the whole psoriatic patient population on biological therapy in Hungary

Authors: Pogácsás L et al.

Summary: This retrospective Hungarian study compared the persistence rate and predictors of persistence for TNF-α and interleukin 12/23 inhibitors in 1263 psoriasis patients over 46 months. Kaplan-Meier analysis indicated that the overall persistence rate for four biologicals was >60% after 3 years. Ustekinumab had the highest persistence rate at 3 years (67.8%) and was superior to the TNF-α inhibitors. Males had higher persistence rates than females, (mean persistence rate 50.8%; p < 0.05). Cox regression indicated that male patients had higher persistence than females (HR 0.76; p < 0.05; 95% CI 0.63-0.92).

Comment: As we have an increasing range of biologic agents to choose from I find myself thinking more and more about how to select the best agent, in the absence of biomarkers, for my individual patients. Equally we need to think about which medications are more likely than not to be continually taken by our patients. There is significantly more expense in patients initiating a treatment than being maintained on a treatment. Therefore switching patients from one drug to the other frequently is in the end more expensive to the community. Numerous studies reported over the years have demonstrated that patients who have had more biological therapies prescribed are less likely to respond. This is a Hungarian study and Hungary does not have a plethora of biologic agents to choose from. This study specifically compares ustekinumab with the TNF-α inhibitors. Overall the persistence rate for the four biologic agents studied exceeded 60%, but ustekinumab had a higher persistence rate than the TNF-α inhibitors. Males had higher persistence rates than females, but age, therapy-naive status and use of concomitant methotrexate did not have an effect on drug survival.

Reference: J Dermatolog Treat. 2017;28(7):635-41
Abstract
Biologic treatments for elderly patients with psoriasis

Authors: Momose M et al.

Summary: Another retrospective study examined the safety and efficacy of biological therapy (adalimumab n = 5; ustekinumab n = 22) over >1 year in elderly (>75 years old) Japanese psoriasis patients. Treatment was discontinued in eight patients; two developed cancer, one was transferred to hospital; five experienced bone fracture, intestinal perforation, fatal cerebral haemorrhage, decrepitude, or hepatopathy after prophylactic tuberculosis treatment. Efficacy, based on PASI 75 score, was 76.9% after 16 weeks (n = 26), 88.0% after 24 weeks (n = 25) and 90.5% after 52 weeks (n = 21).

Comment: This is a study out of Japan, which has a significantly high percentage of elderly in their population. This is a retrospective study looking at patients >75 years old with psoriasis. Their patient group consisted of only 27 patients aged 75-88 years who were being treated with biologic agents for over 1 year. These were divided into five cases treated with adalimumab and 22 cases with ustekinumab. Eight patients discontinued treatment. A 75% PASI reduction was shown at week 16 in 76.9%, at week 24 in 88% and at week 52 in 90.5%. They concluded that biologic treatment shows efficacy in elderly patients, however, there was an increased frequency of adverse events which require quite rigorous observation and monitoring.


A randomized, double-blind, placebo-controlled trial of the effect of monthly vitamin D supplementation in mild psoriasis

Authors: Jarrett P et al.

Summary: This sub-study of a large RCT examined the effect in adults with mild psoriasis aged 50-84 years, of vitamin D supplementation (100,000 IU monthly; n = 23) versus placebo (n = 42) over 12 months. At baseline there was no difference between groups in mean baseline 25-hydroxyvitamin D level (65.7 nmol/L). At the end of the 12 month trial there was no difference in any psoriasis outcome measures between placebo and vitamin D recipients; mean PASI scores 2.2 (95% CI 1.4-3.0) versus 2.1 (95% CI 1.0-3.2), mean Physicians Global Assessment 1.4 (95% CI 1.1-1.7) versus 1.5 (95% CI 1.1-1.9); mean Psoriasis Disability Index 2.1 (95% CI 0.9-3.2) versus 1.9 (95% CI 0.4-3.4), and mean Dermatology Life Quality Index 2.5 (95% CI 1.4-3.6) versus 2.0 (95% CI 0.5-3.4).

Comment: I find this an interesting study considering the media and population interest in vitamin D in our community. Adults aged 50-84 years were invited to participate in a psoriasis sub-study over 12 months. Vitamin D supplementation (100,000 IU per month) was given. 23 patients were allocated to vitamin D, and 42 to placebo. There were no significant differences in baseline between the two groups. At the conclusion at 12 months, there were also no significant differences between the treatment groups in all of the psoriasis outcome measures. Vitamin D supplementation was strongly not recommended as a treatment for mild psoriasis.

Reference: J Dermatol Treat. 2017;Sept 9 [Epub ahead of print]

Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry

Authors: Fiorentino D et al.

Summary: This nested case-control analysis of data from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) was conducted to assess the effect of systemic psoriasis treatment on malignancy risk using 252 malignancy cases and 1008 control patients. Multivariable conditional logistic regression, with adjustment for confounders, indicated that treatment with methotrexate or ustekinumab was not associated with increased malignancy risk, but longer-term (>12 months) treatment with a TNF-α inhibitor was associated with increased risk (OR 1.54; 95% CI 1.10-2.15; p = 0.01).

Comment: An American study from Stanford looking at the effects of psoriasis. The patient group was drawn from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) which records biologic and systemic therapies. 12,090 patients were followed. Exposure was defined as one or more doses of study therapy within 12 months of malignancy onset. There was further stratification by duration of therapy. Study therapies included methotrexate, ustekinumab and TNF-α inhibitors. 252 malignancy cases were identified and 1008 controls were matched. The conclusion was that long-term (>12 months) treatment with a TNF-α inhibitor, but not methotrexate or ustekinumab, may increase risk of malignancy in patients with psoriasis.


Serious infections among a large cohort of subjects with systemically treated psoriasis

Authors: Dobry AS et al.

Summary: Yet another retrospective analysis, this time using data from Kaiser Permanente Northern California health plan members (n = 5889) to determine the serious infection rates in psoriasis patients receiving biological versus non-biological systemic agents. Over 29,717 person-years of follow-up, there was an increased overall risk of serious infection after biological versus non-biological treatment (adjusted [age, sex, ethnicity] hazard ratio [aHR] 1.31; 95% CI 1.02-1.68). The risk was elevated for skin and soft tissue infection (aHR 1.75; 95% CI 1.19-2.56) and meningitis (aHR 9.22; 95% CI 1.77-48.10) during periods of biological therapy.

Comment: A further study out in America from Massachusetts General Hospital, Harvard Medical School and Kaiser Permanente Northern California. Kaiser Permanente has a very large database, 5889 adult members of this health plan with psoriasis who had ever been treated with systemic therapy were assessed for serious infections. The results after adjusting for age, sex, race/ethnicity and comorbidities revealed a significant increased risk for overall serious infection amongst patients treated with biologics as compared to those treated with non-biologics, with a significantly elevated risk for skin and soft tissue infection and meningitis during periods of active biologic use.


Systematic review and meta-analysis of the association between psoriasis and metabolic syndrome

Authors: Rodriguez-Zúñiga JM and Garcia-Penondo HA

Summary: This systematic review and meta-analysis used data from observational studies to evaluate the relationship between psoriasis and metabolic syndrome in adults. In total, 14 studies (n = 25,042) were combined in a random effects model meta-analysis and indicated that metabolic syndrome occurred in 31.4% of psoriasis patients (OR 1.42; 95% CI 1.28-1.65). Studies from the Middle East reported a greater risk for metabolic syndrome (OR 1.76; 95% CI 0.86-2.67) than those from Europe (OR 1.40; 95% CI 2.25-1.55).

Comment: This is a study out of Peru that did a meta-analysis of 14 published studies. A total of 25,042 patients with psoriasis were analysed. Metabolic Syndrome was present in 31.4% of the total patients with psoriasis. Middle Eastern studies (namely Israel, Turkey, and Lebanon) reported a greater risk for metabolic syndrome than European studies (in Germany, Italy, the United Kingdom, Norway, and Denmark). We are all aware of metabolic syndrome. Certainly I would think in my patients that these rates would have been much higher.


Switching of biologics in psoriasis: Reasons and results

Authors: Honda H et al.

Summary: This retrospective analysis of 51 cases requiring a switch of biological therapy for inefficacy or adverse events examined the effectiveness of this strategy. Therapies included infliximab, adalimumab and ustekinumab. Reasons for switching included inefficacy and adverse events, and there were 15 cases of primary failure, 23 cases of secondary failure and eight infusion reactions. Among 49 patients who switched biologics for inefficacy and adverse events, mean PASI score at week 16 was 4.3 with first-line therapy and 2.9 with second-line therapy (p < 0.05).

Comment: This is a study out of a major centre in Tokyo Japan. It addresses the reasons behind switching from one biologic to another as well as the results of having done so. They retrospectively assessed 275 patients treated with biologics between January 2010 and December 2014 from their institution. 51 patients required a switch to another biologic. The first-line therapies that were ineffective were infliximab (n = 26), adalimumab (n = 18) and ustekinumab (n = 7). Second-line therapies were infliximab (n = 5), adalimumab (n = 21) and ustekinumab (n = 25). The highest numbers of patients were switched for inefficacy of medication (n = 38), adverse events (n = 11) and other reasons (n = 2). Primary failure was present in 15 patients and secondary failure in 23 patients. Eight patients developed infusion reactions which could have been due to infliximab.

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Serum human beta-defensin-2 is a possible biomarker for monitoring response to JAK inhibitor in psoriasis patients

Authors: Jin T et al.

Summary: This Chinese study was conducted to determine the correlation between serum human beta-defensin-2 (HBD-2) levels and the response in 18 psoriasis patients to the JAK inhibitor tofacitinib for 16 weeks. PASI score declined (p < 0.05) after tofacitinib 5 or 10 mg twice daily treatment. Serum HBD-2 levels decreased after tofacitinib 10 mg bid versus baseline levels and were lower than in placebo-treated patients (p < 0.05). The correlation between HBD-2 levels and PASI was moderate (r = 0.52; p < 0.01). A serum HBD-2 level cut-off of 125 pg/ml identified mild versus moderate-to-severe psoriasis according to receiver operating characteristic curve analysis.

Comment: Research for biomarkers persists. This is a study looking at JAK inhibitors, specifically tofacitinib, a drug that is not available in Australia for cutaneous psoriasis patients. It is used by our rheumatological colleagues. Presently it and the JAK family are being investigated as treatments for alopecia areata. This study is out of China where only 18 patients were assessed in a placebo-controlled trial. The dose of tofacitinib was 5 or 10 mg bid. This study continued for 16 weeks. Serum HBD-2 levels significantly decreased in patients treated with tofacitinib 10 mg bid compared with baseline and the placebo treated patients. A significant correlation was found between this defensin and PASI response. The conclusion was that serum HBD-2 might be a possible biomarker for monitoring psoriasis treatment.

Reference: Dermatology 2017;233(2-3):164-69

Efficacy and safety of ixekizumab for the treatment of moderate-to-severe plaque psoriasis: Results through 108 weeks of a randomized, controlled phase 3 clinical trial (UNCOVER-3)

Authors: Blauvelt A et al.

Summary: The randomised, controlled phase III UNCOVER-3 trial, tested the use of ixekizumab 80 mg every 2 or 4 weeks, etanercept 50 mg twice weekly, or placebo in 1346 patients with moderate-to-severe plaque psoriasis. Patients in a long-term extension were switched to ixekizumab every 4 weeks after 12 weeks of treatment. In patients receiving the recommended dosage (ixekizumab 80 mg every 2 weeks between weeks 0-12 and every 4 weeks thereafter; n = 385), the 108-week response rate was 88.3%, and the modified MI rate was 83.6%. The 108-week response rate was 83.8%, and the modified MI rate was 82.6%. The 108-week response rate for a static PGA score of 0 or 1 in the as-observed, MI and modified MI analyses were 82.6%, 78.3% and 74.1%. During the long-term extension, a total of 1077 (84.5%) patients reported ≥1 treatment-emergent adverse event; 85% were mild or moderate. The discontinuation rate resulting from adverse events was 6.4%.

Comment: Ixekizumab was released on our PBS in the first quarter of 2017. Therefore it is a medication that is relatively new, with limited long-term data. This is a report of the results at 108 weeks from the pivotal study UNCOVER-3. Improvement in baseline PASI was 82.6% using an as-observed calculation. Also utilising MI a result of 78.3% was recorded and with modified MI 74.1% was recorded. The discontinuation rate because of adverse events was 6.4% which is higher than what I have experienced in my patient cohort; however, Australia has not used the medication for this length of time.


Secukinumab sustains good efficacy and favourable safety in moderate-to-severe psoriasis after up to 3 years of treatment: results from a double-blind extension study

Authors: Bissonnette R et al.

Summary: This analysis of data from a long-term extension of the placebo-controlled, 52-week SCULPTURE study of secukinumab 300 mg treatment every 4 weeks, determined the 3-year efficacy and safety of secukinumab in 168 patients with moderate-to-severe psoriasis. Secukinumab 300 mg at a fixed-interval schedule (every 4 weeks) maintained a high efficacy at the end of 3 years with a PASI 90 response rate of 63.8%, and a PASI 100 response rate of 42.6%. Mean absolute PASI score remained low (2-4) from week 52 to week 152; 68.3% of patients reported no impact of skin disease on their lives (DLOI or 1) at 140 weeks.

Comment: Secukinumab was released in late 2015. This is a review from the pivotal study, SCULPTURE, with data now collected and analysed as at 3 years. Patients were treated in two groups: One group of 168 patients received secukinumab 300 mg as a fixed interval schedule every 4 weeks as we use it in Australia. The other 172 received secukinumab 300 mg with re-treatment as needed. In this study, patients were withdrawn from secukinumab and received the placebo until the start of relapse at which time monthly treatment was reinstated. In conclusion, the fixed interval treatment gave sustained higher responses and improved quality of life. No further safety concerns through 3 years were reported.


Secukinumab is the most efficient treatment for achieving clear skin in psoriatic patients: a cost-consequence study from the Spanish National Health Service

Authors: Puig L et al.

Summary: This pharmacoeconomic analysis compared the cost consequence of biological agents (etanercept, infliximab, adalimumab, ustekinumab, secukinumab) in patients with moderate-to-severe psoriasis from the perspective of the Spanish National Health System (drug treatment costs only; patients with PASI <75 at week 10-16 switched to another agent) using a decision tree with a two-year time horizon. Secukinumab had the lowest annual cost per patient with PASI 90 (cost per responder), followed by infliximab and ustekinumab, and treatment sequences initiated with secukinumab were the most efficient, having the lowest number needed to treat and cost per responder.

Comment: This is a study out of Spain regarding cost-efficient treatment. It is always very difficult comparing cost between different health systems. Spain has a subsidised national system where dermatologists are employees of the State and the Government regulates who receives therapy and what therapies are available. The biologics outlined in this study were etanercept, infliximab, adalimumab, ustekinumab and secukinumab. Please note that ixekizumab was not part of this study. Efficacy at week 24 was considered the highest possible efficacy for each drug and assumed to remain constant throughout the 2-year period. They concluded that secukinumab monotherapy was associated with the lowest cost per responder followed by infliximab and ustekinumab. Although annual cost for treatment is similar for all drugs there was a large difference in the costs per responder.

Reference: J Dermatol Treat. 2017;Oct 5 [Epub ahead of print]