Psoriasis Research Review™

Making Education Easy

Issue 9 – 2012

In this issue:

Abbreviations used in this issue

BMI = body mass index
BSA = body surface area
MTX = methotrexate
PGA = Physicians' Global Assessment
PASI = Psoriasis Area and Severity Index
RCT = randomised controlled trial

Welcome to the ninth edition of Psoriasis Research Review.

Highlights of this issue include findings that pharmacologically active long-chain methotrexate polyglutamates accumulate in patients with psoriasis and reach steady state by 24 weeks; this has clinical implications for our patients. We also have an interesting observational study of juvenile psoriasis, and a valuable review of infusion reactions with infliximab. Recent research also shows that patients with obstructive sleep apnoea are at increased risk for psoriasis, patients with psoriasis are at increased risk for hypertension, and vigorous physical activity can reduce the risk of psoriasis in women.

I hope you find these and the other papers I've selected useful in your clinical practice, and I welcome any feedback.

Kind Regards,

Dr Samuel Zagarella

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Methotrexate polyglutamates as a marker of patient compliance and clinical response in psoriasis: a single-centre prospective study

Authors: Woolf R et al

Summary: This study determined the pattern of erythrocyte methotrexate polyglutamates (MTXPG1–5) in patients taking oral methotrexate for psoriasis, and investigated the use of MTXPGs as markers of compliance and/or clinical response. 55 adult patients with chronic plaque psoriasis were initiated on weekly oral methotrexate. Erythrocyte MTXPG1–5 concentrations were measured at weeks 4, 8, 12, 24 and 52 using high-performance liquid chromatography. All MTXPG1–5 species were detected at week 4 of therapy and steady state for long-chain MTXPG3–5 and total MTXPG1–5 was reached by week 24. MTXPG3 was the predominant MTXPG species from week 12 onwards and reflected overall polyglutamate status. There was no significant association between MTXPG concentrations and responder status or adverse events. In conclusion, MTXPG1–5 concentrations accumulate in patients with psoriasis and could be useful for monitoring patient compliance.

Comment: Methotrexate is an antifolate prodrug that is actively transported into target cells in its monoglutamate form (MTXPG1). In nucleated cells, methotrexate is polyglutamated by the enzyme FPGS to form activated methotrexate polyglutamates (MTXPG2–7); MTXPG1–5 account for 99.6% of intracellular MTXPGs. MTX has been used to treat psoriasis since the 1960s, however, approximately 40% of patients fail to achieve PASI 75 response by 16 weeks, and up to 30% of patients have toxicity. These authors are the first to describe the relationship between intracellular concentrations of MTXPGs and clinical response in patients with psoriasis. Erythrocyte MTXPG concentrations were measured prospectively in 55 patients with moderate to severe chronic plaque psoriasis on weekly oral methotrexate. MTXPG3 was found to be the predominant species at week 12 and was reflective of overall MTXPG concentrations. Steady-state concentration of all MTXPGs was achieved by week 24. However, no correlation between MTXPG concentrations and either clinical response or toxicity was demonstrated in this small study. Now that these authors have shown that a steady state in MTXPG3 was reached by 24 weeks with little variability between patients, there is a potential for MTXPG3 concentrations to be used as an indicator of patient adherence to therapy. This is the first study to demonstrate the prospective accumulation of MTXPG1–5 in patients with psoriasis. An important finding is that the more pharmacologically active long-chain MTXPG concentrations increased with ongoing treatment, reaching steady state by 24 weeks, which has clinical implications for our patients.

Reference: Brit J Dermatol 2012;167(1):165-173
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2133.2012.10881.x/abstract

The influence of treatments in daily clinical practice on the Children's Dermatology Life Quality Index in juvenile psoriasis: a longitudinal study from the Child-CAPTURE patient registry

Authors: Oostveen A et al

Summary: This study evaluated the impact of juvenile psoriasis on quality of life (QOL). 125 children with juvenile psoriasis were assessed by the Children's Dermatology Life Quality Index (CDLQI) and the PASI and were found to have mean scores of 7.5 and 7.0, respectively. Itching and treatment problems had the highest impact on QOL. Assessment of 137 treatment episodes in 85 patients found that all treatments contributed to a significant decline in total CDLQI score; the largest decrease was seen with dithranol and systemic treatments. Reductions in itch and sleep disturbance were the highest positive outcomes of treatment. In conclusion, treatments in daily clinical practice had a positive influence on QOL in children with juvenile psoriasis.

Comment: Juvenile psoriasis causes a significant negative impact on mental health and QOL of those affected. This trial, the first prospective, cross-sectional and longitudinal, observational study on this topic, confirmed the negative impact of juvenile psoriasis on QOL, and also demonstrated a positive influence of treatments on the CDLQI in a cohort of children with psoriasis. The authors found that itch and sleep disturbance caused the highest impact on QOL. In addition, they found that the adolescents (≥12 years) had significantly more problems with issues of clothes and sport compared with the younger children. A significant decline in total CDLQI score was found for all treatments, with the highest improvement in CDLQI for dithranol, followed by systemic and other topical treatments. The systemic treatments analysed in this study were methotrexate and etanercept.

Reference: Brit J Dermatol 2012;167(1):145-149
http://tinyurl.com/9fwjz35

Infliximab for the treatment of psoriasis in the UK: 9 years' experience of infusion reactions at a single centre

Authors: Wee J et al

Summary: This UK study evaluated the incidence of infusion reactions associated with infliximab in patients with severe chronic plaque psoriasis treated at a tertiary dermatology centre. Case notes for all 59 patients who received an infliximab infusion at the centre in 2001–2010 were reviewed. Patients received a total of 858 infliximab infusions (1–43 infusions per patient). Infusion reactions occurred in 16.9% of patients at a rate of 1.5%. Mild, moderate and severe acute reactions occurred in 0.6%, 0.3% and 0.3% of infliximab infusions, respectively. 56% of patients received concomitant systemic treatments during the infliximab treatment (41% received oral methotrexate). 27% of patients who received infliximab alone had an infusion reaction, compared with 4% of those who received concomitant methotrexate (p=0.05). In conclusion, the risk of infusion reactions in our cohort of patients was low and may be reduced by concomitant methotrexate.

Comment: This retrospective review of infusion reactions with infliximab is valuable and gives us some useful information, which has caused the authors to change their infusion protocols. They found a low incidence (1.5%) of both acute and delayed infusion reactions. The severe reactions occurred early on in treatment with two of the three cases manifesting during the third infusion. None of the affected patients who received further infusions continued with treatment successfully, because of a lack of treatment efficacy. This finding suggests that the development of an infusion reaction could be a predictor of treatment failure in patients with psoriasis, similar to that reported with Crohn's disease. Concomitant methotrexate has been shown to reduce the incidence of infusion reactions in patients with rheumatoid arthritis and Crohn's disease, and the data from this study appear to support this, although the significance is limited by the small number of patients involved, the retrospective nature of the study, and the lack of randomisation. The authors now routinely give concomitant methotrexate 7.5mg weekly when initiating on infliximab unless contraindicated. Accelerated infusions are being practised in rheumatology and gastroenterology. A large rheumatology study reviewed the safety of shortening infusion times after the first four infusions, if tolerated without an infusion reaction. The fifth to tenth infusions were administered over 1-h with a 1-h postinfusion observation period, and subsequent infusions over 30min with 30min of observation. I have found that if reactions occur however, a longer infusion time can help the patient cope with the infusion reaction effects.

Reference: Brit J Dermatol 2012;167(2):411-416
http://tinyurl.com/8kdkxtb

A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis

Authors: Gottlieb A et al

Summary: This study compared the efficacy of etanercept plus methotrexate with that of etanercept alone in patients with moderate to severe plaque psoriasis. 478 patients who had not failed prior methotrexate or tumour necrosis factor-inhibitor therapy received etanercept 50mg twice weekly for 12 weeks followed by 50mg once weekly for 12 weeks and were randomised 1:1 to also receive methotrexate (7.5–15mg weekly) or placebo. The primary endpoint (the proportion of patients achieving ≥75% improvement in PASI at week 24) was achieved in 77.3% of patients in the combination therapy group compared with 60.3% in the monotherapy group (p<0.0001). More patients in the combination therapy group had static PGA of clear/almost clear at week 12 (65.5% vs 47.0%; p=0.01) and week 24 (71.8% vs 54.3%; p=0.01). 74.9% and 59.8% of patients in the combination therapy and monotherapy groups, respectively, reported adverse events. In conclusion, combination therapy with etanercept plus methotrexate had acceptable tolerability and superior efficacy to etanercept monotherapy in patients with moderate to severe psoriasis.

Comment: Although we intuitively may assume that addition of methotrexate to biologic therapy may increase efficacy, it is valuable to have this randomised controlled trial to add evidence to this supposition. The authors also adhered to current recommendations of using all 3 measures of improvement (PASI, PGA, and BSA measurements). Etanercept plus methotrexate was more effective than etanercept monotherapy as measured by a significantly higher PASI 75 at weeks 12 and 24, and higher PASI 90 at weeks 12 and 24. Additionally, the proportion of patients with a static PGA of clear or almost clear was significantly higher for the combination arm than the monotherapy arm at weeks 12 and 24. Improvement in BSA score from baseline to weeks 12 and 24 was numerically higher for the combination arm. The safety and tolerability profiles for both the combination and monotherapy groups were acceptable in this trial. This research adds further support to the practice of adding methotrexate to biologic therapy. Other research shows that methotrexate may reduce infliximab infusion reactions, and may theoretically reduce the formation of anti-drug antibodies thus prolonging efficacy of biologics.

Reference: Brit J Dermatol 2012;167(3):649-657
http://tinyurl.com/98b7u6u

The association between physical activity and the risk of incident psoriasis

Authors: Frankel H et al

Summary: This substudy of the Nurses' Health Study evaluated the association between physical activity and psoriasis in women. 86,655 female nurses who had ever been diagnosed with psoriasis completed detailed physical activity questionnaires at enrollment in 1991, and then again in 1997 and 2001. 1026 cases of incident psoriasis were reported during 14 years of follow-up (1991–2005). After adjustment for confounding factors (age, smoking, and alcohol use), increasing physical activity was inversely associated with the risk of psoriasis. The highest quintile of physical activity had a lower relative risk of psoriasis than the least active quintile (relative risk 0.72; p<0.001 for trend). Vigorous physical activity (≥6 metabolic equivalents) was associated with a reduced risk of psoriasis but walking was not. In conclusion, vigorous physical activity is independently associated with a reduced risk of psoriasis in women.

Comment: This study gives support to other evidence from prospective studies which have demonstrated that higher BMI, weight gain, alcohol intake and smoking are associated with an increased risk of psoriasis. In this cohort of US women, vigorous physical activity was independently associated with a decreased risk of psoriasis. The association between vigorous activity and psoriasis risk remained significant after adjustment for BMI. This is the first study to investigate the independent association between physical activity and psoriasis. Each activity was assigned a metabolic equivalent task (MET) value according to established criteria. Participation in at least 20.9 MET-hours per week of vigorous exercise, the equivalent of 105 minutes of running or 180 minutes of swimming or playing tennis, is associated with a 25% to 30% reduced risk of psoriasis compared with not participating in any vigorous exercise. The observed dose-response gradient with increased physical activity supports a causal association between physical activity and a reduced risk of psoriasis. The strengths of the study included a prospective design, a large cohort size, and detailed physical activity assessments. The limitations include reliance on self-reported psoriasis diagnoses rather than a dermatologist's physical examination.

Reference: Arch Dermatol 2012;148(8):918-924
http://archderm.jamanetwork.com/article.aspx?articleid=1158558

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* 4 = maintenance therapy after 2 induction doses

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*Please note changes to Product Information as **italicised text* in Product Information

REFERENCES: 1. Stelara Approved Product Information. Janssen Cilag Pty Ltd, ABN 47 000 129 975, 1-5 Khartoum Road, Macquarie Park NSW 2113 Australia. Phone: (02) 8875 3333 Fax: (02) 8875 3300.

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Psoriasis and hypertension: a case-control study

Authors: Armesto S et al

Summary: This Spanish case-control study determined whether patients with psoriasis are at increased risk for hypertension. 661 patients with psoriasis (cases) and 661 age- and gender-matched controls were included. Patients with psoriasis had a higher prevalence of hypertension than controls (30.3% vs 21.3%; p<0.001). Multivariate analysis adjusted for age, gender, diabetes, obesity and smoking showed that hypertension was associated with psoriasis (odds ratio 1.44, 95% CI 1.07–1.94). In conclusion, these findings support the association between psoriasis and hypertension.

Comment: Eight of twelve previous studies have supported the association between psoriasis and hypertension. The association has been speculated to be attributed to angiotensin II, which regulates vascular tone and stimulates the release of inflammatory cytokines. The main factors associated with psoriasis and hypertension in men are diabetes and obesity, whereas in women they are smoking and obesity. In this study, the prevalence of hypertension was significantly greater in psoriatic patients compared to controls, with psoriatics having a 60% increased risk of having hypertension. A limitation is that it was a cross-sectional study that does not allow the directionality of the association to be ascertained. The only valid conclusion is that the patients with psoriasis had a higher prevalence of hypertension, independent of the confounding factors introduced. Another limitation is that patients tested were in a tertiary referral centre, which may have skewed the test population to a more severe subgroup of psoriasis patients with more comorbidities. However, the control group was age and gender matched, and diabetes, obesity and smoking were controlled for.

Reference: J Eur Acad Dermatol Venereol 2012;26(6):785-788
http://tinyurl.com/9qs7y2s

Efficacy and safety of biologics in erythrodermic psoriasis: a multicentre, retrospective study

Authors: Viguier M et al for the Groupe Français de Recherche sur le Psoriasis

Summary: This study retrospectively investigated the efficacy and safety of biologics in patients with erythrodermic psoriasis. 28 patients with psoriasis involving at least 90% of BSA who had been evaluated before and after 3 and/or 6 months' treatment with biologics were reviewed. A total of 42 flares of erythrodermic psoriasis had been treated with infliximab (n=24), adalimumab (n=7), etanercept (n=6), ustekinumab (n=3) or efalizumab (n=2). The biologic was administered for up to 48 weeks in 34% of flares. A 75% improvement of BSA or PASI 12–14 weeks after treatment onset was reached in 48% of flares treated with infliximab, 50% treated with adalimumab and 40% treated with etanercept. 12 serious adverse events (7 bacterial infections) occurred during treatment. Biologic treatment was discontinued in 19% of cases because of safety concerns. In conclusion, biologics have good short-term efficacy in patients with erythrodermic psoriasis, but treatment switch due to lack of efficacy or poor tolerability is frequently observed with longer term treatment.

Comment: Up until now, the studies that have gathered data on biologic therapies for psoriasis patients have excluded patients with erythrodermic psoriasis, the most severe form of psoriasis, and so data are lacking on the effectiveness and safety of biologic agents for this potentially life-threatening disease. Now, these investigators have conducted a multicentre, retrospective analysis of 28 patients in the French Psoriasis Group network who had received biologic therapies for flares of erythrodermic psoriasis. Eligible patients had psoriasis covering 90% of their BSA and had disease severity evaluated by BSA or PASI scoring before and after 3 or 6 months of treatment. Patients received infliximab for 24 flares, adalimumab for 7, etanercept for 6, ustekinumab for 3, and efalizumab for 2. A 75% improvement of BSA or PASI scores at 10 to 14 weeks after onset of therapy occurred in 48% of flares treated with infliximab, 50% of flares treated with adalimumab, and 40% of flares treated with etanercept. Nearly 20% of patients experienced serious adverse reactions to therapy. In many patients, therapies were deemed to be ineffective over a longer period of time. The study is limited by the small number of patients enrolled but nevertheless is useful as an introduction to the idea of using biologics in erythrodermic psoriasis. In addition, the use of methotrexate, which is often added to biologic therapy, could be explored in other studies. The high rate of adverse effects in this study, most of which were infections, might be related to the extent of the skin disease rather than to its treatment.

Reference: Br J Dermatol 2012;167(2):417-423
http://tinyurl.com/8d6d82j

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Selection of papers and comments are provided by
Dr Sam Zagarella, Clinical Senior Lecturer, University of Sydney Medical School, Dermatologist, Concord Hospital, Sydney.

Increased risk of psoriasis following obstructive sleep apnea: a longitudinal population-based study

Authors: Yang Y et al

Summary: This study evaluated the risk of psoriasis or psoriatic arthritis in patients with obstructive sleep apnoea (OSA). 2258 patients with OSA and 11,255 age- and gender-matched patients without OSA were followed for 3 years to identify patients who were subsequently diagnosed with psoriasis. Overall, 36 patients (0.27%) had psoriasis during the 3-year follow-up period (0.49% of patients with OSA and 0.22% of patients without OSA). Cox regression analysis adjusted for patients' monthly incomes, geographic location, urbanisation level and obesity showed that the risk of psoriasis during the 3-year follow-up period was 2.30 times greater for patients with OSA than for those without OSA (p=0.022). In conclusion, patients with OSA are at increased risk for developing psoriasis or psoriatic arthritis.

Comment: OSA is associated with obesity, insulin resistance, type 2 diabetes and increased cardiovascular disease risk. Mechanisms underlying the link between OSA and these comorbidities have been postulated to involve sympathetic overactivity, hypercoagulability, and the activation of inflammatory cytokine pathways. Chronic inflammation may be a result of psoriasis or may be a factor in the development of psoriasis. Many studies have identified obesity as a predisposing factor for the development of psoriasis, and many patients with OSA are obese. These investigators examined whether OSA is an independent risk factor for the development of psoriasis. When they controlled for obesity, income level, urban environment and geographic location, they noted that the hazard ratio (2.30) remained significant for development of psoriasis with OSA. There are limitations in this type of study. Here, the researchers were unable to ascertain information about BMI, cigarette smoking, and alcohol consumption. However the findings are interesting. Given the close association between both OSA and psoriasis with obesity and metabolic syndrome, the potential link between the two diseases is certainly worth further exploration.

Reference: Sleep Med 2012;13(3):285-9
http://www.sleep-journal.com/article/S1389-9457(11)00382-0/abstract

Placebo response in relation to clinical trial design: a systematic review and meta-analysis of randomized controlled trials for determining biologic efficacy in psoriasis treatment

Authors: Lamel S et al

Summary: This meta-analysis evaluated study design factors that may contribute to placebo responses in trials of biologics in patients with psoriasis. Data from 31 randomised, placebo controlled trials (n=12,284) that assessed the efficacy of etanercept, infliximab, adalimumab, golimumab, ustekinumab, alefacept or efalizumab in patients with psoriasis or psoriatic arthritis were pooled. PASI 75 was achieved in 48.4% of biologic recipients compared with 4.14% of placebo recipients (odds ratio 23.94; p<0.0001). Binomial regression models showed that placebo responses were affected by treatment indication, randomisation fraction, having a PASI inclusion requirement, and the follow-up period. In conclusion, placebo responses seen in RCTs evaluating biologics in the treatment of psoriasis may be secondary to chronic disease course and factors of clinical trial design.

Comment: In aspiring to practice evidence based medicine, the RCT gives us our highest level of evidence possible. We need to understand all aspects and limitations of this method of research, so that we can better understand and apply its results to our patients. These investigators conducted a systematic review and meta-analysis of RCTs in order to better understand how placebo responses affect the efficacy of biologic drugs in psoriasis. They evaluated 31 trials and found an overall rate of 4.14% placebo response (psoriasis patients who achieved a PASI 75 improvement with placebo). The investigators point to several factors that affect placebo response, including a PASI inclusion requirement, the randomisation fraction, the treatment indication and the follow-up period. They concluded that placebo responses are affected by factors of clinical trial design and implementation.

Reference: Arch Dermatol Res 2012; published online 29 Jul
http://www.springerlink.com/content/455305204832502k/

Why statistics matter: limited inter-rater agreement prevents using the Psoriasis Area and Severity Index as a unique determinant of therapeutic decision in psoriasis

Authors: Gourraud P et al

Summary: Recent systematic reviews on the accuracy of existing psoriasis severity scales (including the PASI) suggest that their validity is not fully characterised. This study evaluated the reliability of the PASI as a determinant for therapeutic decisions in patients with psoriasis. 100 patients were each evaluated by 2 practitioners using PASI, and commonly used statistics were used to assess the inter-rater agreement for the PASI. Statistics such as Pearson's linear correlation coefficient "r" and Spearman's rank correlation coefficient overestimated the inter-rater agreement of PASI when compared with the intra-class correlation coefficient (ICC; r=0.8, ρ=0.7, ICC=0.5). When the analysis was restricted to patients with a PASI<20, inter-rater agreement decreased markedly (r=0.38, ρ=0.41, ICC=0.17) and resulted in unacceptable therapeutic decision agreement (κ=0.38). In conclusion, the validity of the PASI score to influence therapeutic decisions is questionable because it has an asymmetric (skewed) distribution.

Comment: Some other recent commentators have questioned whether the use of PASI score is valid in assessing patient response and entry into trials. It has been suggested by others that both the BSA and PGA scores should be added to the PASI score in the evaluation of psoriasis patients. These investigators add further evidence to support this proposition. They conclude that, because the PASI score has an asymmetric distribution, its inter-rater agreement is severely compromised, resulting in unacceptable therapeutic decision agreement. As pointed to in another paper in this review, this poor reproducibility in assessment of PASI score between physicians has important implications in explaining the placebo response in RCTs of psoriasis patients treated with biologic drugs.

Reference: J Invest Dermatol 2012;132:2171-2175
http://www.nature.com/jid/journal/v132/n9/full/jid2012124a.html