three shades of colour – brown, tan and white – in the same patient. The trichrome lesion evolves naturally to a typical vitiligo macula.[7] The significance of the trichrome nature is unknown, but it is clearly an unstable or transitional pigmentary state, though it may persist for months or even years with little change.[8] Fitzpatrick[6] and Pincus[9] interpreted trichrome vitiligo as suggestive of a gradual centrifugal spread of hypomelanosis or a stepwise depigmentation. However, other reports pointed out that the sharp demarcation between the three areas in their cases, as well as the lack of gradual changes of colour and the stability of the lesions, is inconsistent with the interpretation of trichrome vitiligo as an active centrifugal spreading lesion.[8] Therefore, whether trichrome vitiligo is a temporary phenomenon of active spreading vitiligo, or a hypomelanosis showing an unusual progressive pattern, remains to be defined.[10] Hann *et al.*[10] showed that the lesion of the trichrome vitiligo predominated in unexposed skin. That could be one of the reasons why the characteristic trichrome features appeared, possibly because of the slow progression of the disease.

No citations of trichrome vitiligo of the nail unit were found in the literature, but this does not mean that it does not occur. This case showed a melanocytic lesion in the nail plate, which disappeared after the spread of an achromic vitiligo lesion. Between the initial (brown band) and the final (achromic) lesions, a trichrome (brown, light brown and achromic) aspect was observed, representing, in this case, a progressive stage of vitiligo, the trichrome vitiligo. Clinical history, accurate dermatological examination, dermoscopy findings and histological features were fundamental tools for the diagnosis of the trichrome vitiligo of the nail unit. All of these features may well be missed, and thus more frequent than the current literature suggests. The aim of this paper was to describe a case of trichrome vitiligo of the nail unit, showing its basic features, but indicating that it is, in fact, vitiligo in a progressive phase.

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## Is there an emergent need to modify the desmoglein compensation theory in pemphigus on the basis of Dsg ELISA data and alternative pathogenic mechanisms?

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Madam, We read with interest the recent study by Koga *et al.*[1] and we believe that in light of recent observations, including our data (Table 1), the 'desmoglein compensation theory' as an explanation for the localization of blisters in patients with pemphigus should be revisited.[2–4] Although the disruption of desmoglein (Dsg)-dependent cell adhesion by autoantibodies is the basic pathophysiology underlying blister formation in pemphigus,[2–4] the clinical spectrum does not always mirror this pathogenic process. Three clinical types of pemphigus have been described: the mucosal dominant, cutaneous and mucocutaneous types.[2–4] It must also be noted that Amagai *et al.*[2] had subclassified pemphigus into three subtypes, mucosal dominant pemphigus vulgaris (PV), mucocutaneous PV and pemphigus foliaceus (PF), the last of which is analogous to cutaneous pemphigus. Cutaneous pemphigus includes the rare, true cutaneous PV[5] and PF. In the skin, Dsg1 is expressed throughout the epidermis, but more intensely in the superficial layers. Dsg3 is expressed in the lower part of the epidermis, mainly in the basal and parabasal layers. In the mucous membranes, Dsg1 and Dsg3 are expressed throughout the squamous mucosal epithelia, but the expression level of Dsg1 is much lower than that of Dsg3.[2,3,5] Therefore, sera containing only anti-Dsg1 immunoglobulin G (IgG) cause blisters only in the superficial epidermis where Dsg1 is present without Dsg3 coexpression. This differential expression of antigens in conjunction with the anti-Dsg autoantibody profile, as assessed by enzyme-linked immunosorbent assay (ELISA), was used to propose an elegant concept, 'the desmoglein compensation theory', wherein Dsg1 and Dsg3 compensate for each other when they are coexpressed in the same cell.[2,3] This

**Table 1** Summary of data of anti-desmoglein (Dsg) antibody enzyme-linked immunosorbent assay (ELISA) patterns in relation to pemphigus subtypes

| Study, number of patients (n) | Pure mucosal (PV) | Pure cutaneous[a] (PF/cutaneous PV) | Mucocutaneous (PV) | Negative serology |
|---|---|---|---|---|
| Amagai *et al.*[2] (1999, Japan) n = 67 | Dsg3 = 100%<br>Dsg1 = 0%<br>n = 24 | Dsg1 = 100%<br>n = 23 | Dsg3 = 100%<br>Dsg1 = 100%<br>n = 20 | – |
| Yoshida *et al.*[5] (2005, Japan) n = 5 | – | Dsg3 = 100%<br>Dsg1 = 100% | – | – |
| Arteaga *et al.*[6] (2002, U.S.A.) n = 276 | – | Dsg3 = 5·3%<br>Dsg1 = 94·7% | – | – |
| Jamora *et al.*[7] (2003, U.S.A.) n = 32 | Dsg3 = 82%<br>Dsg1 = 28%<br>n = 11 | Dsg3 = 100%<br>Dsg1 = 71%<br>n = 7 | Dsg3 = 93%<br>Dsg1 = 64%<br>n = 14 | – |
| Zagorodniuk *et al.*[8] (2005, Israel) n = 32 (PV), n = 5 (PF) | Dsg3 = 38%<br>Dsg1 = 8%<br>Dsg3&1 = 15%<br>n = 13 | Dsg1 = 100%<br>n = 5 | Dsg3 = 37%<br>Dsg1 = 11%<br>Dsg3&1 = 47%<br>n = 19 | Antibodies to Dsg3/Dsg1 absent in 19% of cases (6/32) |
| Cunha *et al.*[9] (2006, Brazil) n = 32 | – | Dsg3 = 12%<br>Dsg1 = 91% | – | – |
| Sharma *et al.*[10] (2006, India) n = 27 | Dsg3 = 100%<br>Dsg1 = 100%<br>n = 1 | Dsg3&1 = 67%<br>Dsg1 = 33%<br>n = 6 | Dsg3&1 = 90%<br>Dsg1 = 5%<br>n = 20 | Antibodies to Dsg3/Dsg1 absent in 5% of cases |
| Daneshpazhooh *et al.*[11] (2007, Iran) n = 73 | Dsg3 = 94%<br>Dsg1 = 12%<br>n = 16 | Dsg3 = 100%<br>Dsg1 = 67%<br>n = 6 | Dsg3 = 98%<br>Dsg1 = 94%<br>n = 51 | – |
| Kwon *et al.*[12] (2008, Japan) n = 55 | Dsg3 = 46%<br>n = 43 | Dsg1 = 33%<br>n = 12 | Dsg3 = 46%<br>n = 43 | – |
| Abasq *et al.*[13] (2009, France) n = 26 | Dsg3 = 26%<br>Dsg1 = 42%<br>n = 5 | Dsg3 = 5%<br>Dsg1 = 79%<br>n = 7 | Dsg3 = 66%<br>Dsg1 = 64%<br>n = 14 | – |
| Belloni-Fortina *et al.*[14] (2009, Italy) n = 20 | Dsg3&1 = 25%<br>Dsg3 = 62%<br>n = 8 | Dsg3&1 = 100%<br>n = 3 | Dsg3&1 = 78%<br>Dsg3 = 11%<br>n = 9 | Antibodies to Dsg3/Dsg1 absent in 12% of mucosal and 11% of mucocutaneous types |
| Khandpur S *et al.*[15] (2010, India) n = 54 | Dsg3 = 67%<br>Dsg3&1 = 33%<br>n = 9 | Dsg3&1 = 100%<br>n = 2 | Dsg3&1 = 91%<br>Dsg3 = 7%<br>n = 43 | Antibodies to Dsg3/Dsg1 absent in 2·4% of mucocutaneous type |
| Avgerinou *et al.*[16] (2012, Greece) n = 54 | Dsg3 = 76%<br>Dsg1 = 53% | Dsg3 = 67%<br>Dsg1 = 89% | Dsg3 = 100%<br>Dsg1 = 89% | – |
| Koga H *et al.*[1] (2012, Japan) n = 5 | Dsg1 = 100% (EC3/5)<br>n = 2 | – | Dsg1 = 100% (EC1/2)<br>n = 3<br>Dsc3 (one patient) | – |
| Sardana K *et al.*[b] (2012, India) n = 26 | Dsg3&1 = 67%<br>n = 3 | Dsg3&1 = 100%<br>n = 2 | Dsg3&1 = 95%<br>Dsg3 = 5%<br>n = 21 | Antibodies to Dsg3/Dsg1 absent in 33% of mucosal type |

[a]This includes the rare pure cutaneous PV (pemphigus vulgaris) and PF (pemphigus foliaceus). [b]This is based on our 1-year analysis of ELISA in pemphigus; the data are as yet unpublished. EC, extracellular epitope; Dsc, desmocollin.

concept predicted that anti-Dsg1 IgG leads to cutaneous involvement, anti-Dsg3 IgG is ineffective in causing cutaneous blisters because of coexpressed Dsg1 but causes mucosal lesions, while sera containing both anti-Dsg1 and anti-Dsg3 IgG lead to mucocutaneous lesions.[2,3] This simplistic interpretation is largely based on earlier serological studies.[2,3]

Our analysis was based on a prospective study over a period of 1 year performed in a tertiary referral centre in New Delhi (Table 1). All patients fulfilled the following inclusion criteria: (i) diagnosis of pemphigus based on the presence of mucosal erosions and/or superficial cutaneous blisters, suggestive of PV and PF, respectively; and a histological picture of intraepidermal acantholysis and deposition of IgG, complement component 3, detected by direct immunofluorescence; (ii) serial anti-Dsg1 and anti-Dsg3 antibody ELISA combined with clinical evaluations at various times over the follow-up period; and (iii) minimal follow-up of patients at 3 and 6 months after the initiation of therapy. In total, 30 new cases were analysed and 20 controls were taken to validate the sensitivity of the ELISA. The ELISA used was the EUROIMMUN kit (EUROIMMUN,

Lübeck, Germany) with a cutoff value of Dsg1 and Dsg3 > 20 IU index value. Although the sensitivities of Dsg3 in diagnosing pemphigus (96%) and of Dsg1 in diagnosing PF (100%) were high, an analysis of the existing data[5–16] (Table 1) showed that they did not adhere to the existing hypothesis.[2,3] In the mucocutaneous type a mixed pattern of Dsg3/1 was seen (Table 1), which validates one aspect of the desmoglein compensation theory. The cutaneous type of pemphigus can either be the uncommon pure cutaneous type of PV[5] or the more common PF.[2] In this cutaneous type the majority of the studies,[7,10,11,14–16] including ours, reveal a mixed Dsg3/1 pattern. Contrary to the accepted belief,[2,3] Dsg 3 was found in almost 49% of cases (Table 1).[5–16] In fact, the study that originally described the rare phenotype of the cutaneous type of PV[5] noted the concomitant presence of Dsg3 in all of their patients. The authors conjectured that the anti-Dsg3 IgG autoantibodies probably had a 'weak pathogenic potential', which would be just sufficient to block the Dsg3 adhesive function in the skin, but not potent enough to block the Dsg3 function in mucosa.[5] In the pure mucosal type of pemphigus, the Dsg 1 antibody was noted in 39% of cases (Table 1). A recent study[1] found that the Dsg1 antibody was seen in all the cases of pemphigus with oral involvement, which is contrary to the existing hypothesis.[2,3] In fact, the original study by Amagai *et al.*[2] had used a 'modified mucosal dominant type' definition, wherein scattered or isolated skin blisters or erosions up to 5 cm in diameter were seen. The original mucosal type of pemphigus had also described skin involvement. Thus the Dsg ELISA patterns did not strictly adhere to the clinical morphology.

We statistically analysed the existing data (Wessa P, 2012, version 1.1.23-r7, http://www.wessa.net/) using the two-sample *t*-test ($P < 0{\cdot}05$) and compared the three clinical phenotypes with the Dsg3 and Dsg1 positivity by ELISA. Although the mucosal type had a predominant Dsg3 antibody pattern, over 39% of cases had coexistent Dsg1 antibodies

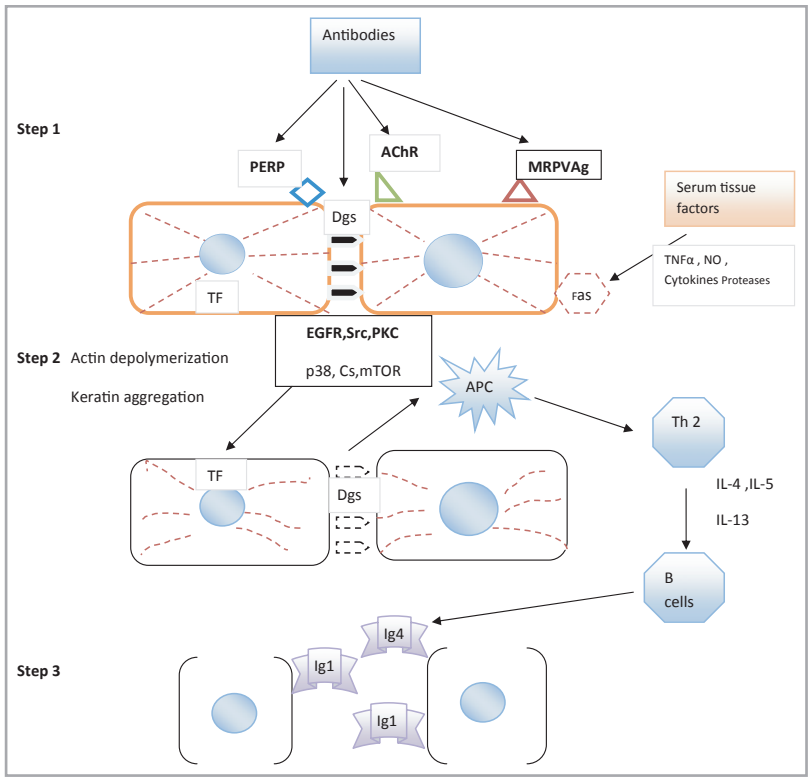


**Fig 1.** A model based on existing data to explain the sequence of acantholysis.[4,21–24] In Step 1, autoantibodies to PERP (peripheral myelin protein 22/growth arrest specific 3 family), cellular AChR (acetylcholine receptors), MRPVAg, (mitochondria-related pemphigus vulgaris antigen) and desmoglein (Dsg) affect the physiological control of polygonal cell shape and intercellular adhesion. This increases phosphorylation of adhesion molecules, with their subsequent dissociation from the adhesion units on the cell membrane, and also initiates extrinsic and intrinsic apoptotic pathways. In Step 2, there is activation of Src, EGFR (epidermal growth factor receptor), p38 mitogen-activated protein kinase (MAPK), Cs (caspases), mammalian target of rapamycin (mTOR) and other signalling elements downstream. This leads to elevation of intracellular $Ca^{2+}$ leading to reorganization of cortical actin filaments, collapse and retraction of the tonofilaments (TFs), which are cleaved by executioner Cs, and dissociation and internalization of intercellular adhesion complexes. Early activation of the Src/EGFR kinase and protein kinase C (PKC)-dependent pathways is pathogenic, while late activation of p38 MAPK is secondary to cell detachment. There is synergistic acantholysis due to the effectors of the apoptotic pathway – FasL and tumour necrosis factor (TNF)-α – as well as proinflammatory and cytotoxic serum and tissue factors. The cytoskeleton collapses and keratinocytes shrink with associated sloughing of desmosomes, eliciting an autoimmune response to the desmosomal antigens, largely mediated by T helper type 2 cells. In Step 3, anti-Dsg antibodies bind to their targets, and by steric hindrance prevent formation of new intercellular junctions.

(Dsg3/1: 69·4%/39·6%, P = 0·09). In the cutaneous type 49% of cases had Dsg3 antibodies (Dsg3/1: 49·1%/82·4%, P = 0·05). In the mucocutaneous type both antibodies were seen (Dsg3/1: 78·1%/67·9%, P = 0·05). In PF we discovered that 25% of cases had a mixed pattern (Dsg1&3), whereas the compensation theory states that patients with cutaneous involvement should have only the Dsg1 antibodies.[2] Koga *et al.*,[1] in their study of patients with PF, also noted mucosal involvement in the presence of Dsg 1 antibodies, which further refutes the existing compensation theory.[2,3] Although this study looked at an uncommon presentation of PF,[1] the existence of other studies[6,9] with the presence of Dsg3 cannot be ignored. Interestingly, in 14% of cases[8,10,14,15] (Table 1) no antibody could be detected. The discordance between the clinical phenotype and the serology has been noted and ranges from 33%[7] to 46%,[8] and this in conjunction with the existing data[5–16] (Table 1) is difficult to explain by the existing theory.[2–4]

One of the predominant drawbacks of ELISA is that it cannot distinguish between the antibodies against pathogenic extracellular 1–2 (EC1–2) epitopes vs. nonpathogenic epitopes, as it tests autoantibodies against the whole Dsg3 molecule.[17] Thus the use of the 'conventional' Dsg3 ELISA is not useful for monitoring the disease, and the results can remain high (Dsg3 > 100) without clinical activity of the disease.[17] Significantly, the use of 'conformational' ELISA[17] contradicts the simplistic interpretation of ELISA[2,3] that forms the basis of the existing hypothesis. Paradoxically, this 'conformational' ELISA is probably not itself perfect, as the recent epitope-specific study[1] found that of the five patients studied, two had antibodies against EC3 and EC5 (mucosa), which are considered to be nonpathogenic, while three had antibodies against EC1

**Table 2** A summary of existing data and hypotheses suggesting a coantigenic role of desmoglein (Dsg) in pemphigus[1,4–23]

| Prevalent data | Newer proposition | Comments |
|---|---|---|
| Antibodies to Dsg as a whole are pathogenic | Antibodies to EC1–2 are pathogenic while those targeting EC 3–5 are 'synergistic and semipathogenic' autoantibodies | ELISA data have to be interpreted with respect to pathogenic epitopes (EC1–2). Thus, the existing ELISA data may not be appropriate for predicting disease pathogenicity |
| Dsg1 and Dsg3 are the primary antigens responsible in pemphigus pathophysiology | The synergistic action of multiple antireceptor and antiadhesion autoantibodies provides a novel paradigm explaining the individual variations in the disease activity and morphology ('multiple hit' hypothesis)[21] | Additional antigens that have been described include desmosomal antigens (Dsg2 and Dsg4, desmocollins 1–3 and desmoplakins 1 and 2); collagen XVII; cell-membrane receptors, such as nicotinic acetylcholine receptor subunits a3 and a9; pemphaxin (also called annexin 31); FceRIa and thyroperoxidase |
| Serological evidence:<br>Dsg1 antibody → PF/ cutaneous pemphigus<br>Dsg3 antibody → mucosal PV<br>Dsg1/3 antibody → mucocutaneous PV | There is evidence that autoantibody specificities and titres do not always relate to the clinical phenotype and disease activity of pemphigus | Our data and recent reports refute this simplistic antibody pattern. The Dsg ELISA patterns do not mirror the clinical presentation |
| Anti-Dsg3 antibody-dependent desmosomal damage causes acantholysis | Various alternative theories have been proposed, including the 'basal cell shrinkage' hypothesis[23] | The 'basal cell shrinkage' hypothesis reconciles the time course of acantholysis in PV. According to this hypothesis: (i) keratinocytes separate because they shrink more than can be held together by desmosomes; (ii) suprabasal clefting occurs because basal cells shrink more than suprabasal keratinocytes; and (iii) pharmacological inhibition of the principal signalling pathways leading to cytoskeletal disorganization should prevent pemphigus |
| Simple steric hindrance within the desmosome due to antibodies leads to acantholysis | Acantholytic keratinocytes are a result of apoptosis and 'oncosis'. Electron microscopic analysis of pemphigus lesions revealed that the loss of cell–cell adhesion occurs in the interdesmosomal membrane portions, and desmosomal disruption is a rather late event<br>The 'apoptolysis hypothesis'[22] links the basal cell shrinkage to suprabasal acantholysis and cell death, and emphasizes that apoptotic enzymes contribute to acantholysis in terms of both molecular events and chronological sequence | The signal that triggers this change is yet to be discovered, but it is probably FasL. The question of whether apoptosis is mediated by anti-Dsg autoantibodies, or whether it is induced by other mechanisms, awaits further investigation |

ELISA, enzyme-linked immunosorbent assay; EC, extracellular epitope; PF, pemphigus foliaceus; PV, pemphigus vulgaris.

and EC2 (skin and mucosa), which are pathogenic. This probably implies that the epitopes do not always predict pathogenicity of the disease and thus the truth lies elsewhere.

The lack of the predictive ability of the Dsg ELISA titres in relation to the clinical phenotype is because of an inordinate focus on Dsg, which is probably merely a 'witness of the disease'.[4] An alternative pathophysiological sequence is proposed (Fig. 1) in view of the following facts:[4,18–23] (i) Dsg is probably not the major factor for adherence of cells; (ii) histological data show that desmosomes remain intact until the late stages of acantholysis; (iii) numerous other antigens, autoantibodies and pathways play a role in pemphigus; and (iv) the antibody detected by ELISA is the 'result' and not the 'cause' of acantholysis in pemphigus.

The full list of 'pemphigus antigens' reported includes over 40 protein bands, but it is believed that the candidates for the pathophysiologically relevant PV and PF antigens are the 130 and 160-kDa polypeptides identified as Dsg 3 and Dsg 1, respectively.[4,18] Consequentially the entire focus is on the role of these antigens, ignoring the other 50 human proteins that have been known to react with the pemphigus autoantibody.[18] Moreover, the existing theory[2,3] has a major flaw in assuming that the integrity of the stratified squamous epithelium enveloping the skin and oral mucosa is dependent entirely on the Dsg 1 and 3 molecules. If this were the case the result would be a disintegration into a single cell suspension in the patients with PV, whereby in patients who develop both anti-Dsg1 and 3 antibodies there is a predominant effect on the suprabasal area.[11] A plethora of contemporary electron microscopic studies of the skin of patients with PV have demonstrated that desmosomes remain intact until the late stages of acantholysis, and thus disintegration is probably an end result of shearing forces produced by collapsing cells[4,18] (Fig. 1).

The most convincing proof that Dsg3 cannot compensate for a loss of desmocollin 3 (Dsc3)[19] is evident in experimental data from a conditional $Dsc3^{null}$ mutant mouse, which exhibits suprabasal acantholysis and overt skin blistering, thus focusing on non-Dsg molecules. In another experimental model,[20] induction of skin blisters in $Dsg3^{-/-}$ neonates by passive transfer of antibodies from patients with PV was studied. In this model, the murine epidermis lacked Dsg3 and the passively transferred PV IgGs lacked the anti-Dsg 1 antibody. As the injected PV antibodies could target only the non-Dsg1 and 3 antigens that mediated and/or regulated keratinocyte adhesion, it provided profound evidence of a non-Dsg antigen. A summary of the existing alternative hypotheses is summarized in Figure 1 and Table 2. A model based on the existing predominant theories[21–23] is given in Figure 1. The production of autoantibodies targeting various antigens leads to acantholysis by weakening the cohesion of neighbouring keratinocytes. The affected keratinocytes shrink, causing desmosomes to be sloughed in the intercellular space, and the antibody response against Dsg is a late event and does not cause acantholysis primarily.[4,17,21–23]

The ELISA test in fact has consistently provided credible proof that the Dsg antigen and antibodies against it do not explain the pathogenesis of the disease. There are many studies from around the world that show that the ELISA titres do not always correlate with the pemphigus disease activity,[13,17,24] relapse[24,25] and exacerbations,[24,25] and can be absent in active disease in patients with PV and appear in remissions.[8,10,12,14,15,26] Although studies have focused on the diagnostic importance of ELISA, there is abundant data[1,5–16] that Dsg1 and 3 testing does not reliably predict the morphological types of pemphigus. Different patients develop distinct constellations of autoantibodies to various antigens (Fig. 1), which, together with the individual's re-epithelialization abilities, determine the clinical severity of the disease, its natural course and response to treatment.[17,18] The Dsg1 and 3 antibodies are sensitive markers for diagnosis of pemphigus,[1–16] but their primary role in the pathogenesis of PF and PV is overestimated.[4,17–23] That is probably the reason why the ELISA values (Dsg 3/1) are not consistent with the pemphigus phenotypes clinically. Thus, in light of the existing evidence (Tables 1 and 2), the existing theory[2,3] should be revisited to focus on other diagnostic and predictive serological tests.

There is no doubt that the Dsg compensation hypothesis is still perfectly suitable for standard textbooks. But, as facts emerge that cannot readily be explained by the current theory, we feel that it is time for *ad hoc* modifications, and an alternative explanation that accounts for all older as well as new observations.

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## Dose escalation may be effective in patients with psoriasis after treatment failure or suboptimal response, but switching to adalimumab is the most cost-effective measure in different scenarios

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MADAM, I read with interest the manuscript by Leonardi *et al.*[1] on dose escalation of adalimumab in patients with psoriasis who did not achieve 50% improvement in the Psoriasis Area and Severity Index (PASI) with respect to baseline. In that study, 12 or 24 weeks after dosage escalation, 26·6% or 38·1% of patients, respectively, were PASI 75 responders, or resumed 40 mg every other week (eow) dosing. Patients for whom dose escalation of adalimumab is most likely to be beneficial appear to be secondary nonresponders with relatively low weight and relatively short disease duration, who are predicted to achieve a 47·8% PASI 75 response rate, whereas dose escalation is least likely to be beneficial in primary nonresponders.[1] In a previous study of dose escalation in 30 patients who did not achieve PASI 50 between weeks 24 and 60 following treatment with adalimumab (40 mg eow for at least 12 weeks) only 17% achieved PASI 75 by week 60.[2]

According to a recent review,[3] dose escalation with biologics typically resulted in greater efficacy than standard dosing among nonresponders, and the ability to 'creep up' the dose of infliximab by increasing the frequency of administration might account for the high patient retention rate observed with this drug in the Danish Dermbio registry.[4] Dose escalation appears to be a rather frequent practice, reported in 10%[5] to 13%[6] of U.S. managed care patients with psoriasis receiving maintenance therapy with etanercept or adalimumab, but the available scientific evidence on the effectiveness of dose escalation in patients with primary failure or suboptimal response is rather scarce. Given the (double) cost of etanercept 50 mg twice weekly, as dosed by many physicians in the first 12 weeks of treatment according to the label, escalation is not an option in the case of primary failure. In an open-label study, patients who did not achieve a PASI 75 response, or who achieved PASI 75 but had significant residual disease after at least 12 weeks of treatment with etanercept 50 mg weekly, were eligible for dose escalation; 64·8% of patients increased their dose accordingly, and approximately 40% of them achieved a PASI 75 response after 24 weeks.[7]

For the alternative strategy (switching), the available scientific evidence is scarce, and mostly restricted to etanercept. Data from prospective registries suggest that PASI 75 can be achieved by 27%, 36% and 54% of patients at weeks 12, 24 and 48, respectively, after switching to adalimumab, following either primary failure, secondary failure or intolerance to etanercept in daily practice.[8] In an open-label study, patients with a Physician's Global Assessment (PGA) worse than 'minimal' following treatment with etanercept for 3–6 months were