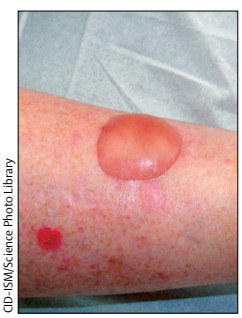
11 Wallace LM, Theou O, Pena F, et al. Social vulnerability as a predictor of mortality and disability: cross-country differences in the Survey of Health, Aging, and Retirement in Europe (SHARE). *Aging Clin Exp Res* 2015; **27:** 365–72.

12 Hajizadeh M, Mitnitski A, Rockwood K. Socioeconomic gradient in health in Canada: is the gap widening or narrowing? *Health Policy* 2016; **120:** 1040–50.

# Doxycycline: a first-line treatment for bullous pemphigoid?



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Bullous pemphigoid is the most common autoimmune blistering skin disease, and incidence is on the rise, due at least in part to its association with older age.[1,2] Treatment of bullous pemphigoid presents a challenge to the clinician, as first-line treatment regimens—either oral corticosteroids or whole body application of super-potent topical steroids—result in substantial morbidity and mortality or present logistical challenges in the elderly.[3]

Few trials have compared therapies for bullous pemphigoid. A previous landmark study[4] found that whole-body topical application of the super-potent corticosteroid clobetasol propionate was at least as effective as oral prednisone for disease control at 3 weeks (and more effective for extensive disease). Notably, clobetasol proprionate treatment was associated with a significant reduction in mortality over 52 weeks compared with high-dose (1 mg/kg per day) but not medium-dose prednisone (0·5 mg/kg per day). Consistent with dose-dependent systemic absorption of topical steroids, reducing the dose of topical steroids provided a similar degree of disease control but with reduced morbidity and mortality.[5] Tetracyclines have been used in dermatology for some time for their anti-inflammatory properties.[6] The only previous study comparing tetracyclines with corticosteroids in bullous pemphigoid was terminated early and the results, although promising, were not statistically significant.[7]

In *The Lancet*, Hywel Williams and colleagues[8] report the results of the largest multicentre trial comparing oral treatments for bullous pemphigoid; the investigators and participating sites should be congratulated for completing this valuable study. Using a non-inferiority trial design, they tested the hypothesis that 200 mg/day oral doxycycline is not inferior in effectiveness to oral prednisolone (0·5 mg/kg per day) and that doxycycline is less likely to result in severe adverse effects. Participants were allowed to apply up to 30 g per week of potent topical corticosteroids to localised lesions for the first 3 weeks, and after 6 weeks. A high proportion of participants were available for analysis at 6 weeks although, perhaps not unexpectedly, a substantial number dropped out by week 52. Rates of withdrawal were balanced between the two treatment groups.

So what were the major findings? The modified intention-to-treat analysis showed that disease control at 6 weeks was achieved by 91% (92 of 101) of participants starting prednisolone compared with 74% (83 of 112) starting doxycycline—an adjusted difference (by baseline severity of bullous pemphigoid and Karnofsky score) of 18·6% (90% CI 11·1–26·1). In terms of safety, this trial underscored the adverse event profile of systemic steroids for bullous pemphigoid: 36% (41 of 113) of participants starting medium-dose oral prednisolone developed a serious adverse event over 52 weeks compared with 18% (22 of 121) of participants starting doxycycline—an adjusted difference of 19·0% (95% CI 7·9–30·1). In agreement with this, and previous studies,[5,7] treatment-related deaths were greater in the prednisolone group (11 deaths) compared with the doxycycline group (three deaths).

So how should these data be interpreted? Some help is provided within the protocol and statistical analysis plan[9] and by an earlier publication from the group that considers, in advance, possible outcomes from this trial.[10] Additionally, it is important to consider how the trial was powered and how the non-inferiority margins were determined and set.[11,12] It appears that the trial was primarily powered to detect a 20% difference in grade 3, 4, and 5 side-effects.[9] Achieving a consensus around the setting of the non-inferiority margin is recognised to be challenging. The authors commendably addressed this in part by undertaking a survey of dermatologists through a national group (the UK Dermatology Clinical Trials Network; appendix p 1[8]).[13] The results of this survey suggested that UK dermatologists were willing to accept a 25% reduction in effectiveness if this was balanced against a 10% reduction in mortality rate for "tetracycline to have potential as a primary treatment for bullous pemphigoid".[13] However, it is not entirely clear how the data from the survey fed into the setting of the primary

endpoints or if the sample size was sufficient to detect a clinically relevant non-inferiority effectiveness margin. Nevertheless, it seems reasonable to move to a broader definition of adverse events (including grades 3–5) and to increase this rate to 20%. Although guidelines for the reporting of non-inferiority trials are not entirely consistent,[11] the non-inferiority margin is often informed by the minimally clinically relevant difference[12] (in this case 25% for effectiveness) such that to reject the null hypothesis (and conclude non-inferiority), the trial would need to provide data where the CI does not cross this boundary. However, the authors interpret the 25% difference as a point estimate and extend the non-inferiority margin to 37%—quite a large difference but one that was achievable from recruiting 128 participants per group. Together, this suggests that the trial might have been underpowered for non-inferiority at a clinically relevant difference of effectiveness.

Overall, the data look interesting and, for now, we are left with the conclusion that doxycycline is non-inferior to prednisolone in effectiveness at a difference of between 11·1% and 26·1% (as set by a 90% CI). The secondary measures of effectiveness at 6 weeks also supported a difference of more than 30% in favour of prednisolone and the Kaplan-Meier curve of time to change in treatment (appendix p 10)[8] clearly favours oral prednisolone over doxycycline. It would be interesting to investigate whether any baseline clinical features or biomarkers might differentially predict treatment response. Finally, although the authors aimed to restrict the use of topical corticosteroids for symptomatic relief, we do not know whether the amount applied by both groups was the same. Systemic absorption from topical corticosteroids does occur, and this must be kept in mind when interpreting disease control, morbidity, and mortality.

In conclusion, doxycycline is clearly safer than prednisolone for the treatment of bullous pemphigoid and demonstrates a reduced success rate, based on achieving three or fewer blisters, at 6 weeks. The evidence for non-inferiority is subjective, dependent on the definition of the clinically relevant non-inferiority boundary. However, given the natural history of bullous pemphigoid,[3] and previous responses to topical treatment alone,[4,5] it is rational to deduce that doxycycline is at least partly effective. So how will this trial affect the management of bullous pemphigoid in clinical practice? Importantly, the primary endpoint for effectiveness in this trial was at 6 weeks. So it would seem reasonable to introduce doxycycline initially in combination with potent (or super-potent)[4] topical steroids; if control is inadequate, treatment can then be escalated to systemic steroids (although this was not covered in the trial design). An alternative strategy, identified by the authors as a potential future trial, would be to start all patients on prednisolone to gain initial control, and then consider doxycycline as a potential maintenance treatment—with patients randomly assigned to continuation of oral corticosteroids or doxycycline.

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1 Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris—incidence and mortality in the UK: population based cohort study. *BMJ* 2008; **337:** a180.
2 Ren Z, Hsu DY, Brieva J, et al. Hospitalization, inpatient burden and comorbidities associated with bullous pemphigoid in the USA. *Br J Dermatol* 2017; **176:** 87–99.
3 Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet* 2013; **381:** 320–32.
4 Joly P, Roujeau JC, Benichou J, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 2002; **346:** 321–27.
5 Joly P, Roujeau JC, Benichou J, et al. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. *J Invest Dermatol* 2009; **129:** 1681–87.
6 Perret LJ, Tait CP. Non-antibiotic properties of tetracyclines and their clinical application in dermatology. *Australas J Dermatol* 2014; **55:** 111–18.
7 Fivenson DP, Breneman DL, Rosen GB, Hersh CS, Cardone S, Mutasim D. Nicotinamide and tetracycline therapy of bullous pemphigoid. *Arch Dermatol* 1994; **130:** 753–58.
8 Williams HC, Wojnarowska F, Kirtschig G, et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. *Lancet* 2017; published online March 6. http://dx.doi.org/10.1016/S0140-6736(17)30560-3.
9 UK Dermatology Clinical Trials Network. The Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) Study. 2015. http://www.nottingham.ac.uk/research/groups/cebd/projects/5rareandother/blistertrial.aspx (accessed Feb 14, 2017).
10 Bratton DJ, Williams HC, Kahan BC, Phillips PP, Nunn AJ. When inferiority meets non-inferiority: implications for interim analyses. *Clin Trials* 2012; **9:** 605–09.
11 Rehal S, Morris TP, Fielding K, Carpenter JR, Phillips PP. Non-inferiority trials: are they inferior? A systematic review of reporting in major medical journals. *BMJ* Open 2016; **6:** e012594.

12 Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012; **308:** 2594–604.

13 Taghipour K, Mohd Mustapa MF, Highet AS, Venning VA, Kirtschig G. The approach of dermatologists in the UK to the treatment of bullous pemphigoid: results of a national survey. *Clin Exp Dermatol* 2013; **38:** 311–13.

# The Global Financing Facility—towards a new way of financing for development

There are many uncertainties in global health. Major policy changes risk affecting women's reproductive health, internal displacement and refugee crises are raging in many parts of the world, and weak public health systems are not readily responsive to emerging health threats. Many countries face fragility, conflict, and economic upheavals. But there is also inspiration and hope in the amazing resilience of communities, as seen in post-Ebola west African countries, and in the power of voice and collective action among informed citizens who are advocating for sexual and reproductive health and rights for all women. Most importantly, we have a unique opportunity to make an indelible and irreversible impact on the favourable odds of women, children, and adolescents surviving and thriving.[1,2]

For more on the **Global Financing Facility** see https://www.globalfinancingfacility.org/our-approach

In recent decades, some of the world's poorest countries, with much support from donors, have made progress in improving the health of their people. But they will be unprepared today and for the future without more coordinated and aligned country-driven efforts to invest in delivering the highest impact health interventions, addressing systems barriers, and tackling social determinants of health. They can save and improve many more lives, and could do so more efficiently, with greater reach, equity, and sustainability. Smart, scaled, and sustainable financing is needed to support these countries' efforts to save and improve the lives of women, children, and adolescents in their poorest communities, which calls for a transformational change in financing for development.

To respond to the tide of global change and prepare for the new development era, the UN, in partnership with the World Bank Group, launched the Global Financing Facility (GFF), the financing arm of *Every Woman Every Child* at the Third International Financing for Development Conference in 2015. The GFF is a new financing model for a different way of investing in health and development (panel). It uses a multistakeholder approach under country leadership, aiming to bring together the contributions in expertise and domestic and international resources of the World Bank Group, the UN, the Bill & Melinda Gates Foundation, The Partnership for Maternal, Newborn, Child and Adolescent Health (PMNCH), Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, bilateral donors, private sector

### *Panel:* Who is the GFF?

The Global Financing Facility (GFF) has been designed as a facility with country ownership at the heart. A country platform brings together the stakeholders who are part of the GFF, under government leadership. In most countries this is an existing structure, but a few countries have decided that no existing structure is quite right and have created a new platform for the GFF to ensure inclusivity and transparency.

The composition of these platforms differs in each of the GFF countries, but they all engage key donors, UN agencies, multilateral financiers (particularly, Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the World Bank), civil society organisations, and the private sector. In Kenya, for example, the partners' consortium includes the UK's Department for International Development, Japan International Cooperation Agency, Danida, UNAIDS, UN Population Fund, UNICEF, UN Women, United States Agency for International Development (USAID), WHO, the World Bank, and others. Civil society plays an important role in advocacy and accountability as well as in service delivery. More concerted efforts are needed to ensure that all aspects of the GFF process benefit from the engagement of civil society organisations, especially to hold all accountable.

Some countries have complemented the work of a formal country platform with additional broad-based consultations. In Cameroon, for example, the launch of the GFF process brought together approximately 200 people from various government ministries (and different administrative levels, with participation from government staff from across the country), civil society representatives, the private sector, and the full gamut of international partners in the country. Subsequent consultations were attended by 100 or more stakeholders, and dedicated events were held with groups such as the private sector. As the country has shifted into implementation in four priority regions, local level consultations are being held in those regions, chaired by regional governors to ensure a wide ownership of the process.

To help support and catalyse this, a multidonor trust fund—the GFF Trust Fund—has been established at the World Bank through generous contributions from the Governments of Canada and Norway and the Bill & Melinda Gates Foundation. Operationally, resources from the GFF Trust Fund are linked with concessional financing from the World Bank Group. To date, these have been linked in a ratio of US$1 from the trust fund to more than US$4 of concessional financing, reflecting grants signed in Cameroon, the Democratic Republic of Congo, Guatemala, Kenya, Liberia, Nigeria, Tanzania, and Uganda. Grants to Bangladesh, Ethiopia, Guinea, Mozambique, Myanmar, Senegal, and Vietnam have been or will be approved by the Bank's Board in 2017.