

The cost-effectiveness of a novel soluble beta-glucan gel

Objective: Wounds that have stalled healing are costly in terms of patient morbidity and increase in use of material and financial resources. A natural polymer beta-glucans has been incorporated into a methylcellulose gel to provide a topical gel designed to accelerate healing in wounds where it has stalled. Although the gel provides an environment conducive to moist wound healing the active agent, beta-glucans, activate the innate immune response.

Method: Using a Markov cohort simulation model, data were extrapolated from a double-blind randomised trial to evaluate the economic benefits of the soluble beta-glucan (SBG) gel in the treatment of diabetic foot ulcers (DFUs).

Results: Over an annual budget cycle, SBG gel is expected to heal 94% of wounds compared with 78% when given standard care. It

also healed wounds more quickly, with the average expected healed weeks 34.4 in the SBG gel group, compared with 24.7 methylcellulose dressing group. In our model this leads to a cost saving over an annual budget cycle of £503 per patient. Note: healed weeks refers to the number of weeks when the wound has healed during the 12-week period and should not be confused with weeks to healing.

Conclusion: The shorter healing time associated with the SBG gel treatment leads to a cost saving because fewer weeks of treatment are required to heal the wound, suggesting this is a promising new cost-effective option for the treatment of DFUs.

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beta-glucan gel • cost-effective • accelerated healing • diabetic foot ulcer

This paper explores the natural polymer beta-glucan, its role in wound care and how a bioactive class III dressing based on bioactive soluble beta-glucan gel offers a cost-effective approach in the management of dry to moderately exuding dermal wounds. Soluble beta-glucan (SBG) gel is available as Woulgan Biogel (Biotec Pharmacon ASA, Tromsø, Norway)

It is generally accepted that uncomplicated acute wounds heal promptly, do not incur financial costs over and above those associated with standard care and do not add unnecessarily to the human 'cost' in terms of increased morbidity. The annual cost of wound care to the NHS, excluding surgical wounds that heal within four weeks of surgery, has been estimated to be in the region of £5.3 billion per annum.² When adjusting for the treatment of associated comorbidities this figure is reduced but, nonetheless, remains substantial at £4.5–5.1 billion per annum. In a Canadian descriptive study of home care patients in 2002 it was found that up to 76% of chronic wound patients had three or more comorbidities³ and in a more recent UK study the mean number of comorbidities found was 3.9 per patient.²

Wounds that present over a longer period can give rise to a range of concerns for the patient. These may include: restricted mobility, social isolation, dressing leakage, malodour, pain, and bulky or unsightly dressings that can inhibit choice of clothes or foot wear.

The adverse impact on quality of life, together with the increased risk of infection that accompanies an open wound, compounds the urgency to achieve timely closure. In addition, the considerable costs associated with the management of chronic wounds place a heavy burden on the health-care provider.^{4,5}

Beta-glucan gel

The SBG gel is a sterile, homogenous viscous gel that contains SBG, glycerol, carboxymethylcellulose, and water. The beta-glucan is extracted from *Saccharomyces cerevisiae* (baker's yeast), by a patented method⁶ that results in a soluble β -1,3/1,6-glucan⁷.

The SBG gel is supplied in 4-gram tubes and intended for use on dry to moderately exuding wounds that have failed to progress under standard care in the preceding four weeks. The SBG gel application is compatible with compression bandaging or offloading devices.⁸ Normally, the dressing should be changed twice per week. In line with good clinical practice wound progress should be monitored weekly.

Chemistry and biological action

Beta-glucans are a heterogeneous group of natural polymers found in the cell walls of bacteria, yeast, fungi and algae, in grains (oats, barley, rye, wheat), and in seaweed.^{9–11} Where differences exist between beta-glucans this is a result of variances in their source, solubility, structure, molecular weight and polymer charge.¹²

Beta-glucans have attracted attention because they belong to a group of physiologically active compounds called biological response modifiers (BRMs). They

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have extensive treatment applications in health care not only in humans but also in invertebrates, rodents, fish and domestic farm animals.¹³ Human health-care interventions with SBGs include those for cancer, diabetes, hypercholesterolaemia, metabolic syndrome, allergic rhinitis, and a marked capability to modulate the immune system.^{10,14–17} They have been used as an adjuvant to immunomodulatory therapy in cancer treatment since 1980¹⁸ and are reported to be effective against bacterial and protozoal infections in experimental models.^{14,19} SBG has been found to be a powerful immunomodulator in animal models.^{20,21}

Immune modulation

SBG are not present or synthesised in mammals. Therefore, in terms of the innate and adaptive immune system they are recognised as 'foreign' if introduced to a host²² and this leads to an influx of macrophages.¹⁵ Macrophages are important wound cleansers that debride the wound of devitalised tissue and dead neutrophils through phagocytosis.²³ They also express a range of growth factors,^{24,25} thereby supporting cellular proliferation, angiogenesis and deposition of the extracellular matrix leading to re-epithelialisation and an increase in wound tensile strength.²⁶ In fact, macrophage activity has been shown to play a fundamental role in the inflammatory, proliferative and remodelling phases of healing.²³ A summary of macrophage activation by SBG may be seen in Fig 1.

Cost-effectiveness of bioactive beta-glucan gel

In health care, the demand for effective interventions will always exceed the supply of resources. Budget holders therefore have to consider the merits of an intervention in terms of effectiveness and cost-effectiveness²⁷ if they are to achieve best value for money. As large-scale randomised controlled trials are not always viable from a time or cost perspective, and as study outcomes may not have been considered with reference to specific endpoints, researchers may seek an alternative approach and undertake modelling studies in order to provide guidance on 'does it work?' and 'does it represent value for money?'²⁸ Analytical modelling is an accepted method used to determine cost-effectiveness profiles and can be helpful in extrapolating intermediate clinical endpoints to final outcomes where the relationship between intermediate outcomes and long-term prognoses is unlikely to be linear, and to combine evidence from head-to-head comparisons with evidence from placebo-controlled trials.²⁹

To date no studies have been undertaken to evaluate the economic benefits of the SBG gel, and for this reason a cost-effectiveness model was developed. The economic model is a Markov cohort simulation populated using patient-level data from the randomised controlled study conducted by Zykova et al.⁷

Methods

Study design

In the study of Zykova et al. 60 patients with type 1 or 2 diabetes were randomised to receive standard care plus either SBG gel or a methylcellulose (Dow Chemical/Colorcon Ltd, Dartford UK) dressing as topical treatments for their DFUs.⁷ Control and experimental dressings were applied three times weekly up to 12 weeks and a total of 54 patients, 27 in each arm, completed the study. The primary endpoint was time to complete healing as determined by the time point when complete closure was achieved. Each week of the evaluation, the investigators assessed the wound for its response to treatment, defined as complete response, partial response, no response and progressive disease.

Secondary endpoints included the number of ulcers that had healed, percentage weekly change in ulcer size, treatment response as defined by investigator (current ulcer status compared with the previous assessment), percentage change in ulcer size (last visit – visit 1). The number of ulcers healed within the study period was defined as those that achieved closure by week 12.

Description of the economic model

A summary of the characteristics of the economic model is shown in Table 1. The economic analysis compares two treatments: standard of care plus either SBG gel or Intrasite Gel (carboxymethylcellulose gel, Smith & Nephew). This carboxymethylcellulose gel (methylcellulose gel) was used as a proxy for the generic methylcellulose dressing (which is not available in the UK) used in the Zykova et al.⁷ study as it is the nearest equivalent product available in the UK. It is a colourless transparent aqueous gel containing 2.3% modified carboxymethylcellulose polymer together with propylene glycol (20%), a humectant and preservative.³⁰

In addition to an analysis based on the 12-week trial and in line with the National Institute for Health and Care Excellence (NICE) methods guide,³¹ the economic analysis also includes the cost-effectiveness over a one-year period. NICE guidance recommends that the time horizon of the analysis should be long enough to capture all of the relevant costs and outcomes associated with a new technology. A one-year horizon was chosen to reflect an annual budget cycle.

Weekly assessments carried out in the clinical trial⁷ recorded the state of the ulcer and response to treatment, and the economic model simulates the transition of wounds between one of four health states reflecting progress towards healing:

- No response (static)
- Partial response (improving)
- Complete response (healed)
- Progressive disease (deteriorating).

Weekly costs were assigned to each of these health states. Information on the health state of the ulcer was available for each patient and ulcer in the trial (some patients had more than one ulcer) and for each of the 12 weeks of assessment. These patient-level data were

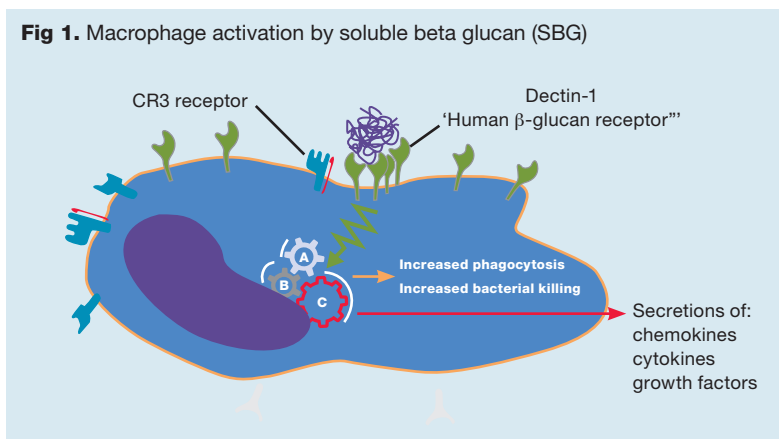


Table 1. Economic model specification

Patients	Adults (age ≥18 years) with type 1 or type 2 diabetes mellitus, wound located on the foot or lower leg present for at least 4 weeks and not more than 2 years (in line with inclusion criteria for the clinical trial)
Time horizon	12 weeks and 1 year
Model structure	Markov cohort simulation with weekly cycle length
Health states	Based on treatment response: static, improving, healed, deteriorating
Perspective	Costs falling on community health services in the UK. Costs include: nurse time, dressings and other materials
Comparators	Standard of care plus soluble beta-glucan gel, dressings changed three times weekly Standard of care plus methylcellulose gel, dressings changed three times weekly
Outcome measures	Percent healed Mean weeks in a healed state Mean cost per patient Incremental cost-effectiveness ratio (ICER) = incremental cost per additional week healed
Sensitivity analysis	Scenario analysis

also used to estimate weekly transition probabilities between health states, and to construct a transition matrix, which was used to extrapolate outcomes up to one year.

Resource use and cost

Information on ulcer status and response to treatment was used to estimate weekly treatment costs by multiplying the number of patients in each health state by the relevant weekly health state cost. Costs include the time of a community nurse and GP, the costs of SBG gel or methylcellulose gel, and the costs of dressings and other materials. Details of sources of costs are shown in Table 2.

The weekly costs by health state and treatment for the base-case analysis are shown in Table 3. Base case assumptions are:

- Dressing changes are three times weekly for both

treatments, in line with the clinical trial protocol

- Dressings are changed by a nurse at a home visit (41 minutes per change, including travel time)
- SBG gel and methylcellulose gel are indicated for single use and the base-case analysis assumes that a new tube is required for each dressing change
- Once ulcer healing is confirmed, no further dressing changes or nurse contacts are required. This is a simplifying assumption. In practice one or two nurse contacts might be required to confirm healing before treatment is discontinued
- If the ulcer deteriorates, use of SBG gel or methylcellulose gel is discontinued. Nurse visits and dressing changes continue and one GP consultation is assumed for each week the ulcer is deemed to have deteriorated. This is a conservative assumption. In practice a range of tests and additional investigations are likely to be ordered to identify the cause of the deterioration.

Results

In the Zykova et al randomised controlled trial in the per-protocol (PP) population at 12 weeks 56% of the ulcers healed with the SBG gel and 37% with methylcellulose dressing.⁷ The economic model precisely replicates these healing rates. Using patient-level data from the trial makes it possible to identify the exact week in which healing occurred and to estimate the average number of weeks healed in the 12-week period (the number of weeks healed refers to the number of weeks during the 12-week period when the wound is healed).

During the 12-week period patients treated with the SBG gel, on average required 2.13 weeks less treatment. The average expected weeks healed for the SBG gel-treated patients was 3.96 compared with 1.83 for patients treated with standard care alone.

The 12-week costing analysis is based directly on patient-level data from the clinical trial. The mean treatment cost per patient over the 12-week analysis period was £1,459.80 for the SBG gel and £1,358.90 for the methylcellulose. Therefore the incremental cost of SBG gel over this period was £100.90 per patient. The incremental cost per additional healed week is £47.37 (£101/2.13) (Table 4). Results of the base-case and one-year extrapolation analysis are shown in Tables 4 and 5.

Extrapolation of the trial data provides a more meaningful view compared with the 12-week costing analysis because the annual cost impact is likely to be more relevant to a budget-holder. The analysis was extrapolated from 12 to 52 weeks by applying weekly transition probabilities estimated from the trial data. Over an annual budget cycle, treatment with the SBG gel is expected to heal 94% of wounds compared with 78% with standard of care (Table 5). SBG gel treatment also healed wounds more quickly, and the average expected healed weeks for patients treated with SBG gel was 34.37, compared with 24.65 for methylcellulose gel, and the incremental benefit (weeks healed) was 9.73

Table 2. Resource use-unit costs

Community nurse time	Cost of a community nurse Mean average cost for a face-to-face contact=£39. This is equivalent to a total of 41 minutes, including travel time (@£57 per hour)	Personal Social Services Research Unit, 2014 ³² in Table 10.1
GP time	Cost of one 11.7 minute GP surgery consultation	Personal Social Services Research Unit, 2014 ³² in Table 10.8b
Soluble beta-glucan gel	£20 per 4g tube	Manufacturer
Methylcellulose gel	£1.80 per 8g tube (smallest available Smith and Nephew)	Drug Tariff Part IXA, Hydrogel dressings, sterile. ³³ accessed June, 2015
Wound dressing Allevyn non-adhesive	£1.25 for 5 cm x 5 cm (mean ulcer area in the per protocol population in the trial=4.39 cm ² (Woulgan); 2.87 cm ² (placebo)	Drug Tariff Part IXA, Polyurethane foam film dressing-without adhesive border. ³⁵ Accessed June, 2015
Other materials	Sterile dressing pack (DT specification, 10 dressing pack)=£0.53 Gloves (Vitrex gloves) = £3.89 per 50	Drug Tariff Part IXA, Sterile dressing packs. ³³ accessed June, 2015 Drug Tariff Part IXA, Nitrile gloves. [†] Accessed June, 2015

weeks over a 52-week period (Table 5). Thus, over a one-year period, patients treated with the SBG gel are, on average, expected to require 9 weeks less treatment compared with those receiving standard care with methylcellulose. The shorter healing time with the SBG gel leads directly to a cost saving because fewer weeks of treatment are required to heal the wound. Over the annual period, the SBG gel is expected to be cost saving to the extent of £503 per patient and to heal more wounds (94% versus 78%).

Scenario analysis

The scenario analysis varies each of the assumptions underlying the estimates of health state costs by

treatment (Table 3), these assumptions and the results of this process are shown in Table 6. The base-case demonstrates that results are most sensitive to the time horizon. The longer the time horizon, the greater the difference in the net budget impact of SBG gel compared with methylcellulose gel. In the base-case and each of the scenarios tested the SBG gel is cost saving over an annual budget cycle (Table 6).

Results are very sensitive to the fact that the product should not be re-used. Both the SBG gel and methylcellulose gel are indicated for single use, but allowing for the possibility where a single tube may be used for the same patient for up to three dressing changes, the SBG gel is cost saving within the 12-week period of the trial.

Table 3. Resource use. Weekly health state costs by treatment

Ulcer health state	Weekly frequency of dressing change	Nurse time per dressing change	Tubes per dressing change	Other materials per dressing change	GP consultation per week	Total cost per week
Static						
Soluble beta-glucan gel	3	£39	£20 (1 tube)	£1.94	0	£182.82
Methylcellulose gel	3	£39	£1.80 (1 tube)	£1.94	0	£128.22
Improving						
Soluble beta-glucan gel	3	£39	£20	£1.94	0	£182.67
Methylcellulose gel	3	£39	£1.80	£1.94	0	£128.07
Healed						
Soluble beta-glucan gel	0	0	0	0	0	£0
Methylcellulose gel	0	0	0	0	0	£0
Deteriorating						
Soluble beta-glucan gel	3	£39	£0	£1.94	£46	£168.82
Methylcellulose gel	3	£39	£0	£1.94	£46	£168.82

Table 4. Results of the 12 week analysis (per protocol population)

	Ulcers healed %	Average weeks healed per patient	Average weeks of treatment	Cost per patient	Additional weeks healed per patient	Incremental cost per week healed
Soluble beta-glucan gel	56%	3.96	8.04	£1459.80	+2.13	£47.37
Methylcellulose gel	37%	1.83	10.17	£1358.90	–	–

Table 5. Results extrapolation to 1 year (per protocol population)

	Ulcers healed	Average weeks healed per patient	Average weeks of treatment	Cost per patient	Additional weeks healed per patient	Incremental cost per week healed	Incremental cost per additional week healed
	Percentage	Mean per patient	Mean per patient	Mean per patient	Per patient	Per patient	ICER
Soluble beta-glucan gel	94%	34.37	17.63	£3190.60	+9.73	-£503.20	Dominates*
Methylcellulose gel	78%	24.65	27.35	£3693.80	–	–	–

*A dominant treatment option is one that is both less costly (saving £503) and results in better health outcomes (heal more wounds, 94% versus 78%) than the comparator treatment (the former 'dominates' the latter)

Table 6. Scenario analysis

	Incremental cost (soluble beta-glucan gel versus methylcellulose gel)		ICER: Incremental cost per additional week healed (soluble beta-glucan gel versus methylcellulose gel)	
	12 weeks	1 year	12 weeks	1 year
Base-case	+£100	-£503	£47.37	*Dominates
Frequency of dressing change: Base-case is 3 x weekly for both treatments				
2 x weekly (all)	+£55.0	-£375	£25.80	Dominates
2 x weekly and 3 x weekly if the ulcer deteriorates	+£21.9	-£481	£10.30	Dominates
Reuse of soluble beta-glucan gel and methylcellulose gel: In the base-case, both products are single-use. In practice, a single tube could be used for the same patient for up to 3 applications (one week)				
One tube per week (3 applications per tube)	-£165.3	-£1043	Dominates	Dominates
Confirmation of healing: In the base-case nurse visits stop once the ulcer is healed. In practice some follow-up assessment visits may be required to confirm healing				
Nurse contact monthly	+£122.7	-£151.8	£57.60	Dominates
Adjustment to treatment if the ulcer deteriorates: The base-case assumes that treatment with the current product would stop if the ulcer deteriorates				
Treatment continues for the full period of the analysis even if the ulcer deteriorates	+£128.9	-£402.2	£60.50	Dominates

ICER=incremental cost-effectiveness ratio; *A dominant treatment option is one that is both less costly (saving £503) and results in better health outcomes (heal more wounds, 94% versus 78%) than the comparator treatment (the former 'dominates' the latter)

Results are also sensitive to the frequency of dressing change. The lower the frequency, the lower the net additional cost of the SBG gel. However, patient outcomes assumed in the cost model are based on the clinical trial in which SBG gel was applied three times weekly. It should not be automatically assumed that outcomes would be the same if the frequency of application were lower.

Limitations

Limitations of the analysis include the relatively small numbers in each treatment arm and the fact that the trial comparator is not a treatment that is currently used in UK clinical practice. The extrapolation of the 12-week trial data to an annual budget cycle may be considered a methodological limitation. However, this short 12-week period reduces some of the uncertainty sometimes associated with extrapolations from trial data. A Markov approach is commonly used to model the cost-effectiveness of health-care interventions, but one limitation of this method is the fact that it assumes transitions between health states are independent of the time spent in the previous state. In this analysis, for example, the model assumes that the probability of moving from partial response (improving) to complete response (healed) is not dependent on the time spent in the partial response state. The introduction of more complex health states or the use of time-dependent probabilities was not undertaken, primarily on the basis that it would add little to the overall conclusions. The Zykova study⁷ limited recruitment to DFUs and therefore extrapolation of cost-effectiveness data to other wound types is not possible.

The extrapolation from 12 weeks to 12 months in the analysis is an important driver of results and a number

of assumptions have to be made. Future work should ensure that there is a longer period of follow-up so that extrapolation is unnecessary.

Conclusion

The evidence available from the Zykova et al. clinical trial⁷ demonstrates that SBG gel is expected to lead to an improvement in patient outcomes through faster ulcer healing. The economic modelling study, with patient data drawn from the trial, showed that patients treated with the SBG gel are expected to require fewer treatment weeks compared with those who receive standard care with methylcellulose gel. The implications of this is that the shorter healing time leads directly to a cost saving because fewer weeks of treatment are required to heal the wound. The SBG gel is a promising new cost-effective option in the treatment of DFUs. **JWC**

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Reflective questions

- Have you considered immune modulation as a viable treatment
- Does application of the soluble beta-glucan gel on wounds where healing has stalled require specialist skills?
- Dressing choice - in your search for evidence do you only consider efficacy or do you also search for evidence on cost-effectiveness?
- Considered the concept of 'healed weeks' and how it differs from 'weeks to healing'?

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