Cost-effectiveness of Apligraf in the treatment of venous leg ulcers

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The treatment of patients with venous leg ulcers (VLU) using one application of a skin substitute (Apligraft), in addition to a 4-layer bandage system, was examined.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised typical patients with the following characteristics:

- man or woman, usually older;
- leg swelling present at the end of the day for years;
- history of ulcer;
- possible history of phlebitis;
- if female, previous pregnancy;
- presence of ulcer in medial malleolus region for at least 4 weeks;
- presence of ulcer measuring 3 by 4 cm with healthy granulation tissue base;
- presence of palpable dorsalis pedis pulse (ankle brachial index > 0.8; no significant arterial disease);
- possible presence of leg pain that interferes with daily activities;
- patients had undergone local therapy and compression alternatives without significant healing.

Setting
The setting was an outpatient clinic. The economic study was carried out in Canada.

Dates to which data relate
Some effectiveness and resource use data were derived from studies published between 1993 and 1998. The fiscal year 1995/1996 was used for some costs.
Source of effectiveness data
The effectiveness evidence was derived from experts' opinions.

Modelling
A computer-based model was constructed to evaluate the clinical and economic outcomes associated with the two treatments in a hypothetical cohort of 1,000 patients. Two time horizons were considered, 3 months and 6 months. The 3-month horizon was chosen because it represented the typical length of follow-up of the clinical trials, while the 6-month period was representative of a longer timeframe. Events included ulcer days, infections and infection severity. Recurrences were allowed only in the 6-month model.

Methods used to derive estimates of effectiveness
A panel of five dermatologists and two family practitioners from across Canada was contacted, using a modified Delphi panel, to identify the model inputs related to the effectiveness and safety estimates. Data from three published studies (including one clinical trial) were provided to the experts. Several assumptions were made to determine the parameters for the 6-month model from the values used in the 3-month model.

Estimates of effectiveness and key assumptions
The panel estimated that:

- the healing rates were 60% with the 4-layer bandage and 67.5% with the 4-layer bandage plus skin substitute;
- the mean times to 100% wound closure were 8 weeks (without skin substitute) and 3.7 weeks (with skin substitute), respectively;
- the percentage of patients who experienced recurrence among those who healed was 4% in both groups;
- the mean time between healing and recurrence was 30 days in both groups;
- the times to reach 100% closure for recurrences were 4 weeks (without skin substitute) and 1.25 weeks (with skin substitute); and
- the numbers of mild, moderate and severe infections were 15, 7.5 and 1.3, respectively, with the 4-layer bandage, and 15, 14 and 3 the 4-layer bandage plus skin substitute.

In the 6-month model, it was assumed that no additional skin substitute was applied in the 4- to 6-month period. Further, three scenarios were considered for those patients who experienced an ulcer during months 4 to 6. In scenario 1, the mean ulcer days per patient in months 4 to 6 remained different for both arms and was set at the same mean ulcer days per patient as in months 1 to 3. In scenario 2, the mean ulcer days per patients in months 4 to 6 was set the same for both arms and equal to 4-layer bandage arm in months 1 to 3. In scenario 3, the healing rate in months 4 to 6 for both arms was set at half the rate in months 1 to 3. One application of the skin substitute was assumed.

Measure of benefits used in the economic analysis
The summary benefit measure was the mean number of ulcer days per patients with the two treatments. This was estimated using the decision model.

Direct costs
Discounting was not relevant since the costs were incurred during 6 months. The unit costs were not presented separately from the quantities of resources used. The health services included in the economic evaluation were physician services, pharmaceuticals, home care nurse, home-maker, social worker, occupational therapist, physiotherapist, bandaging supplies, laboratory and diagnostic tests, unit stay and clinic visits. The cost/resource boundary of both the health care system and society was adopted. Resource use was estimated on the basis of experts’
assumptions. The costs came from multiple sources including the Ontario Health Insurance Plan schedule of benefits, the Ontario Drug Benefit Formulary, the financial system of a university database, and a local health care provider. The costs were estimated using 1996 and 1997 prices.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
Indirect costs (i.e. lost patient wages due to VLU) were included in the analysis because a societal perspective was adopted. The indirect costs came from average Canadian industrial aggregate weekly wages. As in the analysis of direct costs, resource use was estimated on the basis of experts’ opinions and 1996/1997 prices were used. Discounting was also not relevant, and the unit costs were not presented separately from the quantities of resources used.

Currency
Canadian dollars (Can$).

Sensitivity analysis
Univariate sensitivity analyses were carried out in the 3-month model, using the societal perspective, to examine the robustness of the incremental cost-effectiveness ratios to variations in the model inputs. The model inputs investigated were the healing rates, time to heal, infection rates, price of the skin substitute, total cost excluding the skin substitute, and time loss from daily activities. No justification for the choice of the ranges of values was provided.

Estimated benefits used in the economic analysis
In the 3-month model, the mean ulcer days per patient were 67 with the 4-layer bandage and 45 with the skin substitute plus 4-layer bandage.

In the 6-month model, the mean ulcer days per patient ranged from 60 to 67 with the skin substitute plus 4-layer bandage, and from 95 to 98 with the 4-layer bandage.

Cost results
In the 3-month model, from a societal perspective, the mean cost per patient was Can$1,758 for the skin substitute plus 4-layer bandage and Can$1,454 for the 4-layer bandage. The corresponding figures from the health care system perspective were Can$1,701 (with skin substitute) and Can$1,386 (without skin substitute), respectively.

In the 6-month model, from a societal perspective, the mean cost per patient ranged from Can$2,087 to Can$2,231 for the skin substitute plus 4-layer bandage, and from Can$2,050 to Can$2,119 with the 4-layer. The corresponding figures from the health care system perspective were Can$2,014 to Can$2,152 (with skin substitute) and Can$1,953 to Can$2,019 (without skin substitute), respectively.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the alternative treatment strategies.

In the 3-month model, the incremental cost per ulcer day averted with skin substitute plus 4-layer bandage over 4-layer bandage alone was Can$14 using both perspectives.

In the 6-month model, the incremental cost per ulcer day averted with skin substitute plus 4-layer bandage over 4-layer bandage alone was less than Can$5 in all scenarios.
The results of the sensitivity analysis showed that the model was generally robust to almost all variations in model inputs. The exception was time loss from usual daily activities, in which case skin substitute plus 4-layer bandage dominated 4-layer bandage alone.

Authors' conclusions
The use of a skin substitute in addition to the 4-layer bandage was more effective but also more costly than the 4-layer bandage alone. Thus, the question was whether Can$14 per ulcer day averted was good value for money for society. The analysis suggested also that the cost-effectiveness of skin substitute plus 4-layer bandage improved over time.

CRD COMMENTARY - Selection of comparators
The authors reported the main treatments for venous ulcers (external support and compression; low versus high compression) and justified the choice of the comparators selected for the analysis. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from experts' opinions and consensus was achieved using a modified Delphi approach. Experts were given published information (including a clinical trial), which was used as the basis upon which to choose model estimates. Each estimate was assigned a score on a 5-point scale, which reflected the validity and uncertainty of the responses. The issue of uncertainty in the model inputs was addressed in the sensitivity analysis, where key estimates were varied.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study and is not comparable with the benefits of other health care interventions. Benefits (as well as costs) were estimated over two different time horizons using a modelling approach.

Validity of estimate of costs
The analysis of the costs was carried out from two different perspectives, which were appropriate. All the relevant categories of costs were included in the analysis. However, a detailed breakdown of the costs was not provided and the unit costs were not presented separately from the quantities of resources used. In fact, there was limited information on the costs. This limits the possibility of replicating the study. The source of the data was provided for all categories of costs. All estimates were treated deterministically and some key economic inputs were varied in the sensitivity analysis. The prices used were reported, which makes reflation exercises in other settings easy.

Other issues
The authors did not compare their findings with those from other studies. They also did not address explicitly the issue of the generalisability of the study results to other settings. Some sensitivity analyses were carried out, which in part enhanced the external validity of the study. However, sensitivity analyses were not performed on the 6-month model inputs.

Implications of the study
The authors suggested that their analysis provides decision-makers with the best estimates of costs and effectiveness of the skin substitute for VLU. However, the current results should be corroborated in a future prospective study.

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