Why have the Health Claims for Probiotics been rejected?

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Outline

- Reasons for rejections
  - *L. casei* Shriota
  - *L. casei* DN 114 001
  - *L. rhamnosus* GG
- EFSA guidance
- Peer review

Probiotics

"Live microorganisms which on ingestion of certain numbers exert health benefits"

Ezendam & Van Loveren, 2007

Health benefits probiotics

- Gastrointestinal effects
- Immunological effects

L. Casei Shirota

Claim (art. 13.5):

Maintenance of URT defense against pathogens by maintaining immune defenses.

Substantiation:

9 pertinent studies

- 3 proprietary studies
- 6 studies unrelated to defense against URTI

L. Casei Shirota
Reasons for rejection

Gleeson et al. (unpublished – now published!)

URTI's in athletes

- Symptom score questionnaire not validated
- High # drop-outs not appropriately taken into account in data analysis

Van Gils et al., 2009 - unpublished

- Pilot trial was underpowered

Van Puyenbroeck et al., 2009 – unpublished

URTI's & Response to Influenza vaccination >65's

- change in primary outcome during the study
- scored symptoms of URTI are non-specific
- post-hoc analysis anti-influenza IgG subjects >80 not preplanned

L. Casei Shirota
Reasons for rejection

3 studies on NK-cell activity – inconclusive

1 study in subjects with seasonal allergic rhinitis:

- antigen-induced IL-5, IL-6, IFN-γ,
- specific IgE and specific IgG

1 study in subjects with HTLV-1 infection

1 study in subjects with alcoholic liver cirrhosis

3 studies in animal models

L. Casei Shirota
Reasons for rejection

Taken together:

- No human study from which conclusion could be drawn (-)
- 1 human study did not support effect *Lc*S on IR against (-) influenza vaccination
- Lack of evidence for mechanism (-)

Conclusion: cause-effect relationship not established

L. Casei DN-114 001

Claim (Art. 14):

Reduction of the presence of *Clostridium difficile* toxins in the gut which reduces the incidence of acute diarrhea

Substantiation:

10 human studies
- 7 published
- 3 unpublished

9 non-human studies
- 8 published
- 1 unpublished

L. Casei DN-114 001
reasons for rejection

- Houldern et al., 2009 – unpublished
  - Non-controlled study
  - Not controlled for other factors of influence on CDAD than Actimel
- Bulpitt et al., 2009 – unpublished
  - Underpowered pilot study
- Bulpitt & Hickson, 2010 – unpublished
  - Recruitment stopped before target sample size (derived from PC) was reached
  - Treatment of missing data not convincing – more conservative scenarios not applied

L. Casei DN-114 001
reasons for rejection

- 1 *in vitro* study on *Lc* DN-114 001 inhibition *C. Difficile*
  - Occurrence effect *in vitro* does not predict effect in vivo
- 5 human studies on kinetics, metabolism & survival *Lc* DN-114 001 and its impact on microbiota during GI-transit
  - Partial survival consistently shown
  - GI-passage without detectable multiplication
- 2 human studies on Actimel and GI infections and GI pathogens other than *C. Difficile*
- 3 studies on effect *Lc* DN-114 001 on microbiota
  - No statistically significant effect on dominant members of faecal microbiota
  - No statistically significant effect on bacterial enzyme activities

L. Casei DN-114 001
reasons for rejection

- 2 animal studies + 3 *in vitro* studies on possible effects of Actimel or *Lc* DN-114 001 in model systems related to immune function and infection
  - Occurrence effect in animals or *in vitro* does not predict effect in vivo

L. Casei DN-114 001
reasons for rejection

Taken together:

- Partial survival *Lc* DN-114 001 during GI-transit (+)
- The only 1 human study showing significant effect had considerable limitations (+/-)
- Mechanistic studies do not support proposed mechanisms (-)
- Data obtained in model systems do not predict occurrence of such effects in humans (-)

- Conclusion: insufficient evidence to establish cause and effect relationship

Lactobacillus rhamnosus GG (LGG)

Claim (art. 13.5)

Maintenance of defense against pathogenic gastrointestinal microorganisms

Substantiation:

- 7 human studies addressing effect LGG on incidence/severity/duration of acute diarrhea
- 2 studies on Traveller's diarrhea
- 2 studies on incidence of diarrhea in free-living children
- 3 studies on incidence diarrhea in hospitalized children (a.o. Hojsak et al., 2010)

Lactobacillus rhamnosus GG (LGG)

Taken together:

- Only 1 out of 5 human intervention study showed effect LGG on GI-infections (*children!!)* (-)
- 2 human intervention studies did not show an effect of LGG on stimulation of protective IR after oral (viral) vaccination (-)

Conclusion:

Cause-effect relationship not established

Rejection of studies
common themes

- Underpowered studies
- Diagnosis of infections
- Symptom score questionnaires not validated
- *Post hoc* analysis not pre-planned
- Treatment of missing data/drop outs
- Biomarkers of immune system unrelated to the claimed effect/proposed mechanisms
- Occurrence effect in animals or *in vitro* does not predict effect *in vivo*

Rejection of applications
overall theme

In clinical trials Probiotics & Infections

- no measure of causative microbiological agent!
- often no relevant biomarker of immune function included

EFSA Guidance

- Drawn from scientific opinions
- Based on the experience gained to date

No measure of causative microbiological agent!

EFSA Guidance

Appropriate outcome measure that is generally considered meaningful:

- No less than 1 log value reduction (2010)
- Relevance of reduction should be justified (2011)

Biomarker - DRRC (art. 14)

E.g. disease risk reduction of *CDAD*

Risk factor/biomarker:

- Reduction in # pathogenic microorganisms in stools
- Reduction in toxins in stools

- Measured in cases as well as in non-cases!?
- Simultaneous occurrence risk factor – disease!

Incidence, duration and/or severity of infection can not serve as evidence for reduction of the risk factor

However, could be supportive of claimed effect

Biomarker General function claim
art. 13.5.

Maintenance of normal defense against pathogens in GI/URT/U tract

Appropriate outcome measures:

- Reduction # pathogenic microorganisms in stools
- Reduction toxins in stools (or other suitable samples)
- Reduction incidence, duration and/or severity
  - Clinician's diagnosis
  - Validated symptom score questionnaires

Supportive evidence GI infections

Supportive evidence from studies on:

- Intestinal permeability
- Production SCFA's
- pH

Insufficient by themselves for substantiation of the claim.

Peer-review & EFSA

Many peer-reviewed studies declined by EFSA

Many scientist said to agree with EFSA's judgement!

Proprietary paper declined by EFSA accepted by peer-review (Gleeson et al. 2011)

Apparently, (many?) scientists do not agree with EFSA's judgement!

Peer-review & EFSA

scientific criteria acceptance peer-reviewed journal
apparently differ from
scientific criteria for health claim substantiation!

Implication

Published studies should be meticulously screened for potential flaws in study methodology before paper can be accepted as pertinent

Newly designed studies should be targeted at HC substantiation

- esp. when collaborating with institutional research group

Thank you!

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