Gene therapy: a concept for the future in medical practice?

The current state

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Keywords
Gene therapy

Summary
Gene therapy is a new therapeutic approach which is tested in numerous diseases connected with either non or only limited therapeutic effects. This paper aims at discussing the actual state of the clinical development of gene-therapy which targets an approval by either the FDA or EMEA. Basis of all the figures and tables presented is a BioMedNet/Medline search reviewing all titles found under the keywords gene therapy and/or clinical development. The review period begins in the year 1992 and ends in 2002. Publications identified were sorted into the following categories: therapeutic areas with gene-therapy activities; indications and diseases with gene-therapy activities; vectors used in gene-therapy and clinical studies using gene-therapy. Only in some indications like breast cancer, colorectal cancer, HIV, and cystic fibrosis a variety of clinical studies had been published indicating a serious attempt to develop the indication for approval. But most developments are still in phase I/II. In all other therapeutic areas no systematic continuous approach was identified. Clinical activities in cardiovascular diseases and in peripheral vascular diseases increased during the preceding five years compared other therapeutic areas.

Gene therapy is defined as introduction of healthy genes via gene transfer agents (vectors) into the genome of patients to treat diseases caused by defective genes. Since more than 15 years growing resources in medicine, molecular biology, and biochemistry are spent on gene therapy. This new therapeutic approach is tested for numerous diseases, if conventional therapy shows no or only limited effect. So far, the tremendous efforts invested resulted in only limited success. None of the gene-therapeutic approaches has succeeded and exerted any permanent impact upon medical practice in any disease.

In this paper the current state in clinical development of gene therapy which targets an approval by either the FDA or EMEA is discussed.

Methods

Basis of all figures and tables presented is a BioMedNet/Medline search reviewing all titles found under the keywords gene-therapy and/or clinical development. Different selection criteria have been applied to clean and sort the publications and to discriminate between articles on new methodology, descriptions of scientific attempts to get first information of gene therapeutic approaches in man and those activities which are part of an clinical development program designed with the attempt to achieve an approval at regulatory bodies and to market the product or a device or a combination of both.

The review period begins in 1992 and ends in 2002. Publications identified by the Medline search were sorted into the following categories:
- all publications found in Medline from 1992 to 2002,
- therapeutic areas with gene-therapy activities,
- indications and diseases with gene-therapy activities,
- vectors used in gene-therapy,
- clinical studies using gene-therapy.
Publication were reviewed whenever necessary to allow the sorting into the right category.

**Results**

**Publications in Medline 1992-2002**

Figure 1 and Table 1a show the increasing number of publications concerning gene-therapy in the preceding decade when the keywords gene-therapy and clinical development are used in BioMedNet/Medline to retrieve appropriate publications. In the early nineties less than 100 articles were found compared to more than 400 articles in 2002. A careful review of the titles and summaries reveal that in an increasing number clinical development and clinical studies are mentioned as a future potential of the work described whereas the work itself is focusing on methodology or on data from animal models. This discrepancy is broadening in the recent years. The number of qualifying articles seems to plateau since 2000 whereas the number of publications focusing on methodological progress is growing extra-proportionally.

**Therapeutic areas, indications and diseases with gene-therapy activities**

All together articles concerning 78 different indications were published during the defined review period indicating the broad variety of potential targets for gene therapy. These indications were assigned to different therapeutic areas as seen in Table 1.

Among the therapeutic areas oncology covers about 50% of all publications followed by rare genetic disorders, as expected, and cardiovascular diseases. Only a few publications were detected focusing on central and peripheral nerve diseases and on metabolic disorders. No tendencies on increased scientific activities were noticed on the latter two therapeutic areas, because of the constant low number of publications, whereas the busiest therapeutic areas show...
a steady increase in the number of annual publications.

 Sorting the different diseases within therapeutic areas, only six could be identified to be summarized as metabolic disorders. Diabetes mellitus was mentioned six times, but mainly in the last two years. Five publications dealt with hypercholesterolaemia in the early years of the observation period. All other indications are cited only one time (Tab. 1b). In central and peripheral nervous system diseases only in Parkinson’s disease and in central nervous system injuries a number of articles were published (6 and 11, respectively). This first publication in this area occurred in 1996 with a declining frequency after 2000. Infectious diseases are dominated by studies on HIV (23 out of 33 publications). All other infectious indications are cited only once or twice during the last decade (Tab. 1c).

 Table 1d shows an overview of the different immunological diseases. Beginning with the early nineties an almost constant number of articles were published on transplantation. 15 publications on rheumatoid arthritis and arthritis are released during the last five years indicating an arising interest in these diseases since the underlying pathomechanisms are better understood. First studies on deficiency of the immune system and restoration of its deficiencies were published since the mid nineties. They certainly have to be seen in the light of work done around HIV. Only little work is seen on other immunological indications.

 Tables 1e and 1f are summarizing the studies performed in haematological and haemostaseological disorders and in cardiovascular diseases. Since the early nineties a constant flow of information is published on the restoration or suppression of the haematopoetic system very closely linked to the work published in oncology (Tab. 2, Tab. 1h). In recent years an increase in publications on haemophilia A an B can be observed.

 The research and development in the cardiovascular field is dominated by work on the ischaemic syndromes shown by an increasing number of publications starting in 1994 and 1995 (40 out of 68 identified publications are focusing on these targets). A new arising area is angiogenesis with
already 18 publications in the preceding seven years.

The most publications were found concerning oncology. 368 (>45%) could be identified with an increasing number each year (>50 publications/year since 2000). Publications on 35 cancer types were found, but as in all other therapeutic areas the vast majority of publication was written on a few cancer types: melanomas (with 24), leukaemia, and lung cancer (with 21 articles each). General publications on gene therapy increased from four (in 1992) to 21 (in 2002).

Table 1g summarizes studies published on rare genetic diseases. They had been an early target for gene therapeutic approaches. Most publications appeared on cystic fibrosis (34 out of 72) over the last nine years. On most of the other diseases there are only one or two publications. Publications focusing on Duchene muscular dystrophy, Fabry disease and lysosomal storage diseases appeared only in 2001 and 2002, whereas publications on Gaucher’s disease were written only in the first half of the nineties with no publication occurring after 1997.

Diseases like acute lung injury, asthma, osteogenesis, osteoporosis, and fracture healing where only a few publications documented so far with no clear pattern identified. 48 publications were allocated to this group.

Vectors for gene-therapy

The grouping shown in Tables 1b-g is artificial and mainly guided by medically defined therapeutic areas and not by the selected methodology or the mechanism of pathophysiological interference. Table 2 gives an overview on vectors used and vehicles mentioned in the cited publications. It is remarkable that retroviruses and adenoviruses are dominating the whole observation period. Whereas the retroviruses were almost constantly used over the years, adenoviruses are used in more and more studies and are clearly dominating the vector scene since 1998. In the recent years some new viruses (e.g. lento viruses) are increasingly used. Non-viral liposome mediated gene transfer has a stable place in 10-15% of the studies. Direct gene transfer is only used in a minority of studies. It never gained any importance during the last 10 years. The same is true but to a lesser extent for the different vaccination approaches.

Clinical studies using gene-therapy

A much smaller number of publications are focusing on the description of the design of clinical studies in the different indications and the clinical phase they are in. Among those the majority of studies are described as planned, less are running and only a view are clinically completed and reported. Nevertheless, publications on 14 non-oncological indications could be identified (Tab. 1h) with no clear tendency of an increase in studies planned and conducted during the recent years. Two and three publications appeared in 1995 and 1996 respectively, then nine publications during the preceding three years of the observation period. No clear focus was recognized. For all indications only one or two studies are described.

In Table 1i the accessible clinical studies in oncological indications are summarized. Twice as many oncology studies could be identified compared to non-oncological gene therapy studies. 17 different cancer
types are described. The first article is published on a study in melanoma patients in 1995. As in non-oncological studies no clear focus could be seen. Four publications deal with breast cancer, three publications each with patients suffering from malignant melanoma and ovarian cancer. All other cancer types are described in one or two publications.

Because from these publications no clear information could be derived to what extent a professional clinical development for later approval was planned or described, another source (What’s in the Pipeline, version 01) was used. As shown in Table 3, 15 products are claimed to be in clinical development:

- one in clinical phase III,
- 10 in clinical phase II,
- 4 in clinical phase I/II, and
- 14 in early phase I.

As big pharmaceutical companies only Aventis and GSK are named. The other are specialized biotechnological companies which usually need at least financial support from large pharmaceutical companies, when they approach the later stages of clinical development. All are still about 2-4 years away from approval and have still a high probability to fail based with regard to the current status of clinical development. The indications targeted are mainly oncological ones (9 out of 14 publications). The non oncological indications are: coronary and peripheral re-stenosis, COPD, and chronic bronchitis, HIV, and cystic fibrosis.

**Discussion**

After a series of failures and the increasing difficulty to raise adequate research funds, it may be speculated that the increased number of review articles and articles focusing on methodology around gene-therapeutic treatment approaches and the increased number of publications of clinical studies reflects the growing urgency to show substantial improvement in the development of applicable gene therapies.

It is obvious that gene therapeutic approaches are tried and under investigation in quite different diseases. However, only some indications, e.g. those concerning oncology (breast cancer, colorectal cancer) and a few non-oncological indications (e.g. HIV, cystic fibrosis) produce a relatively constant number of publications. In all other therapeutic areas no systematic continuous approach was identified.

Compared to the other therapeutic areas only little work is done in metabolic, central and peripheral nervous disease, infectious diseases (besides HIV) and immunology. No tendency is observed for a growing output during the observation period.

**Conclusion**

The literature survey presented here is summarized as follows:

- The number of publications on gene therapy increased steadily in the early nineties to reach a first peak in 2000. 2001 and 2002 showed a decrease in publications.
- Most clinical gene therapies are applied to cancer patients.
- Activities in cardiovascular and peripheral vascular disease increased in the recent years.
- Most clinical developments have not yet reached the final steps for approval. The vast majority of developments are still lingering in phase I/II with a likelihood of reaching the market in <20%.
- The increased knowledge of the impact of the genetic pattern on different diseases has however enriched the diagnostic possibilities. But is of no value for actual therapeutic concepts.

At the time these data were collected to review the actual status of gene therapy and its future potential as impact of the current medical therapy, the Food and Drug Administration put an official hold on
running gene therapy studies which have been commented by A. Pollack (January 15, 2003) as follows:
1. The Food and Drug Administration yesterday suspended 27 gene therapy trials involving several hundred patients after learning that a second child treated in France had developed a condition resembling leukaemia.
2. The agency said it was not aware that any of the patients treated in the 27 American trials had suffered illness similar to that of the infants in France but was nevertheless taking precautions.
3. The temporary halt, the largest such action involving gene therapy trials, is yet another setback to the fledgling field.
4. The field is still shaken from the death of a teenager undergoing gene therapy in 1999 at the University of Pennsylvania and from the first case of leukaemia in an infant in France last year.

References

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