UN SECOL DE IMUNOTERAPIE SPECIFICĂ

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Rezumat

Certificatul de naştere al imunoterapiei specifice a fost lucrarea "Inocularea profilactică împotriva febrei de fân", publicată în "The Lancet" 1911, volumul 177 (pg. 1572-1573). Leonhard Noon şi John Freeman au dezvoltat o nouă modalitate de tratament pentru bolnavii cu rinită alergică la polen. S-a născut o nouă metodă terapeutică specifică bolilor alergice şi care, până în prezent, a rămas singura capabilă să modifice cursul natural al unei alergii. Azi, această metodă se numeşte imunoterapie specifică şi se efectuează cu vaccinuri alergenice. Pe parcursul celor 100 de ani de existenţă, au fost efectuate numeroase studii (in vitro, pe animale, şi pe oameni) legate de preparatele ce pot fi folosite în imunoterapie. De la preparatele apoase, s-a trecut la cele depot, apoi la cele cu alergeni modificaţi (alergoide) sau cu alergeni recombinanţi, toate cu administrare subcutanată. S-au elucidat mecanismele de acţiune ale imunoterapiei. Au fost demonstrate efectele produse pe limfocitele reglatoare (T reg), pe limfocitele Th2, pe IL-4, pe IgE specifice. Eficienţa şi eficacitatea clinică au fost demonstrate în rinită, astm şi anafilaxie la înţepatura de insecte. Azi indicaţiile imunoterapiei specifice se extind: alergia alimentară şi dermatita/eczema atopică. În ultimele două decenii au apărut vaccinurile alergenice cu administrare locală (sublinguale, orale). Deşi au trecut 100 de ani de la prima publicare a unui caz tratat prin imunoterapie specifică, această metodă este încă tânără!

Cuvinte cheie: imunoterapie specifică, 100 ani.

A CENTURY OF SPECIFIC IMMUNOTHERAPY

Abstract

The birth certificate of specific immunotherapy was the article "Prophylactic Inoculation against hay fever", published in "The Lancet" 1911, volume 177 (pg 1572-1573). Leonhard Noon and John Freeman developed a new therapeutic method for hay-fever patients. This was the specific therapy for allergic diseases, the only one able to change the natural course of an allergy. Today this method is named specific immunotherapy and it uses allergenic vaccines. During these 100 years many clinical studies were performed (in vitro, on animals, or on patients) with different vaccines. Aqueous extracts used at the begining were changed to the depot ones and to modified allergens (allergoids), or recombinant allergens, all of them being given subcutaneous. The mechanism of immunotherapy was understood: the effects on Treg, on Th2, on IL-4, on specific IgE were prooven. The efficacy and effectiveness of immunotherapy were shown in clinical trials in rhinitis, asthma, anaphylaxis to hymenoptera. Today the indications for immunotherapy were extended to food allergy, to atopic dermatitis/ eczema. In the last two decades topic vaccines were developed, with sublingual and oral administration. A hundred years have passed since specific immunotherapy emerged, and the method is still young!

Keywords: specific immunotherapy, century.

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Bolile alergice au fost descrise ştiinţific doar în secolul al XIX (descrierea rinitei alergice) [1], deşi în decursul istoriei au fost raportate multe cazuri ce ar putea fi incluse între alergii (de ex. decesul faraonului Menes în urma unei înţepături de insecte ce a dus la şoc anafilactic) [2,3].

La începutul secolului XX s-au introdus în practica medicală şi noi proceduri terapeutice. Astfel s-a născut şi imunoterapia. Anul 1911 este considerat anul creării imunoterapiei, odată cu publicarea în iunie a studiului observaţional al lui Leonhard Noon (Fig. 1) şi John Freeman (Fig. 2) [4]. Acest studiu a fost primul trial clinic realizat pe oameni utilizând un vaccin alergenic, respectiv extract de polen de iarbă (*Phleum pratense*). În articolul de două pagini, cu trei cote bibliografice (Fig. 3) se demonstrează toleranţa la polen prin testul de provocare conjunctival cu polen la cei ce au efectuat imunoterapia, în comparaţie cu lotul fără imunoterapie.

Fig. 1. Leonhard Noon (1878-1911).

Fig. 2. John Freeman (1877-1962).

Terenul pentru "inocularea profilactică" a fost deschis pe mai multe planuri. În secolul XIX o serie de cercetări au demonstrat rolul polenului în producerea rinitei [1]. Primele metode terapeutice de profilaxie au fost create iniţial pentru variolă (Edward Jenner a creat primul vaccin antivariolă în 1773). Au fost făcute încercări de "hiposensibilizare" pentru polen, pentru antigeni proveniţi de la cal, dar unele dintre ele s-au soldat cu efecte secundare severe. Alexandre Besredka a introdus un tratament de inoculare cu alergen la animalele hipersensibilizate, Noon şi Freeman preluând această metodă şi aplicând-o ulterior la pacienţii cu rinită alergică [1].

Noon a decedat la scurt timp după publicarea articolului referitor la rinita la polen, cercetarea efectelor inoculării profilactice fiind continuată de Freeman. Robert Cooke a introdus această metodă terapeutică nouă în Statele Unite ale Americii sub denumirea de "imunizare activă".

De-a lungul celor 100 de ani, această metodă a primit mai multe denumiri: desensibilizare, hiposensibilizare, inoculare profilactică, anti-anafilaxie. În anii 80 s-a introdus termenul de imunoterapie specifică (ITS). Se discută dacă denumirea completă nu ar fi imunoterapie specifică cu alergen (ITSA) (pentru a o diferenţia de imunoterapia specifică cu anticorpi monoclonali anti-IgE).

Azi se acceptă ca definiţie a ITS administrarea unor doze progresiv crescânde ale alergenului specific relevant, pentru tratarea bolilor alergice mediate de IgE, până la o doză de întreţinere, pentru ca pacientul să nu mai prezinte simptome la contactul cu alergenul [6].

Cei 100 de ani de existenţă au marcat diferite aspecte ale studierii şi aplicării imunoterapiei. S-au efectuat numeroase studii legate de mecanismul de acţiune, eficienţa clinică, vaccinurile utilizate, modalitatea de administrare a vaccinurilor, efectele secundare, contraindicaţii etc. La o căutare în baza de date ″Medline″, utilizând cuvintele-cheie "imunoterapie specifică alergenică" apar nu mai puţin de 3482 de articole (190 doar în 2011)!

Dacă Noon şi Freeman au efectuat imunoterapia subcutanat, azi se practică şi administrarea topică (sublinguală – cea mai acceptată, dar şi nazală sau orală). Produsele topice sunt administrate sub formă de picături, spray, tablete. Deşi nu este încă aprobată de FDA, ITS sublinguală se practică în proporţie de 6% de către alergologii americani.

Primul studiu dublu orb controlat placebo, referitor la imunoterapia specifică, a fost publicat doar în 1965 de Lowell şi Franklin [7]. Acest studiu s-a efectuat la pacienţii alergici la polenul de ambrozie. Rezultatele au susţinut eficienţa imunoterapiei.

Imunoterapia specifică a fost administrată în rinitele alergice. Indicaţiile s-au tot lărgit: alergie la veninuri de insecte, la astm bronşic alergic. În ultimii ani se aplică şi la dermatita/eczema atopică [8]. În prezent există numeroase meta-analize (27) legate de eficienţa ITS.

S-au efectuat numeroase evaluări ale efectelor imunologice produse prin ITS. S-a discutat de iniţierea sintezei de imunoglobuline blocante (IgG4), despre modificarea echilibrului între limfocitele Th2 şi Th1, stimularea limfocitelor T reglatoare (Treg) (Tabel I)

History of allergen-specific immunotherapy — Ring and Gutermuth

1572 THE LANCET.] MR. L. NOON: PROPHYLACTIC INOCULATION AGAINST HAY FEVER. [JUNE 10, 1911.

bleeding, and then administer salines. In the other 14 cases so treated the condition of the patients permitted of the delay necessary for preparatory treatment and for the removal of all blood clots from the abdomen.

The crisis having passed, and when the case is first seen subsequent to the formation of a distinct and encapsulated hæmatocele, more conservative treatment is warranted. With rest in bed the majority of such cases undergo complete absorption, the only indication for operative interference being the possibility of secondary rupture of the hæmatocele demanding coeliotomy, or infection of the sac, which is best treated by vaginal incision and drainage. Against an entirely expectant line of treatment the element of time has to be considered, especially with hospital patients. Large hæmatoceles may take weeks to undergo complete absorption, which loss of time may be prevented by the safe proceeding of vaginal incision and drainage. Of my six cases so treated five were typical cases of retro-uterine hæmatocoeles, and the patients left the hospital within three weeks from date of admission. In the remaining case of hæmatoma, abdominal section having shown that the blood was encapsulated in the broad ligament, the abdomen was closed and the case further treated by vaginal incision and drainage.

Dundee.

PROPHYLACTIC INOCULATION AGAINST HAY FEVER.

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HAY fever is a form of recurrent catarrh affecting certain individuals during the months of May, June, and July. It is caused by a soluble toxin found in the pollen of grasses. The patients present the idiosyncrasy of being sensitive to this toxin, which is innocuous to normal individuals. The idiosyncrasy may be detected during any season of the year by dropping a little of an extract of grass pollen into the eye of the suspected individual; a reaction, described more fully below, will be obtained in the case of a hay fever patient, but a normal man will show no effect.

Bostock (1819)[1] recognised the seasonal recurrence of hay fever as separating it from other forms of catarrh. Blackley (1873)[2] advanced much evidence in favour of the pollen theory of its causation, but we owe chiefly to Dunbar (1903)[3] the exhaustive scientific proof of this theory. Dunbar showed that not only all the mucous membranes but even the skin of hay fever patients is sensitive to pollen toxin in a way not shown by normal individuals. He also proved that the injection of the pollen toxin gives rise in animals to the production of an antitoxin having a specific power of neutralising this toxin. Further, in hay fever patients, he showed the occurrence of some of the reactions associated with the production of immunity:—namely, a specific precipitation of pollen extracts by the patient's serum, and the phenomenon of complement deviation, during the hay fever season, and persisting for a short time after this. Pollen toxin is, therefore, a body capable of giving rise to the production of antibodies in animals and even in hay fever patients, subjected to its action. It is also undoubted that hay fever patients sometimes become cured of their idiosyncrasy. The most reasonable explanation of this phenomenon would seem to be, that the cured patients have had the good fortune to develop an active immunity against the toxin, to the action of which they have been liable for so long.

The repeated absorption of toxin at short intervals is, however, more likely to induce a condition of hypersensibility, and this is the more usual fate of the patient, who becomes only more sensitive during each succeeding season. The local application of a specific serum, such as pollantin, offers a reasonable method of treatment, but one which is difficult and laborious, and which is not calculated to bring about a permanent cure. Cures are, indeed, ascribed to the use of this remedy, but admittedly in exceptional cases; and where the conditions are not understood and the experience is not constantly repeated, one must hesitate to attribute the result to the cause cited. On general grounds a much more satisfactory result would be expected from the induction of an active immunity, and it seemed worth while to put this expectation to the test of experiment. The questions to be answered are as to what degree of immunity can be induced in hay fever patients by inoculations of pollen toxin, how these inoculations may best be regulated, and whether the affection can by this means be permanently cured.

With this end in view the experiments here described were undertaken in the past autumn, winter, and spring to study the reaction of hay fever patients towards inoculations of pollen toxin. The off season of the year, when the patients were not exposed to spontaneous inoculations, was favourable to this investigation, as the scheme of dosage was then not liable to be upset by spontaneous absorption of toxin from the air, laden with actively poisonous pollen grains. The plan of experiment was to obtain a numerical measure of the sensitiveness of the patients to the pollen toxin and to observe whether this was increased or decreased by subcutaneous inoculations of various quantities of pollen toxin. These observations can be conveniently carried out by the method described below, and it was found that, with well-regulated dosage, it was possible in every case to raise the patient's resistance, to a marked degree, within the lapse of a few months, while, on the other hand, ill-regulated dosage was at once made evident by a decrease in the resisting power.

The pollen extract used was prepared by Dunbar's method of extraction with distilled water, aided by freezing and thawing several times. The extracts were boiled for ten minutes after having been sealed in glass tubes; this treatment was not found to decrease their activity at all. The pollens tested were grass pollens of different species—*Phleum pratense*, *Poa trivialis*, *Holcus lanatus*, and *Agropyrum cristatum*. These pollens were all found capable of exciting an energetic reaction when instilled into the conjunctival sac of hay fever patients. Timothy grass (*Phleum pratense*) was found to yield the most active extract, and this extract was consequently used throughout the rest of the experiments. One gramme of pollen was extracted with 50 c.c. of water. The activity of this extract may be judged from the fact that one drop of a five thousand-fold dilution is sufficient to excite a distinct reaction in the conjunctiva of the more sensitive patients.

In order to express the strengths of pollen extracts used in testing patients and the doses of pollen toxin given subcutaneously, a unit of pollen toxin has been arbitrarily chosen. This unit is the quantity of pollen toxin which can be extracted from the thousandth part of a milligramme of Phleum pollen, and it has the advantage that all the quantities used can be expressed in whole numbers. The strength of a pollen extract is given below in terms of the number of such units contained in a cubic centimetre of the extract. Extracts of other pollens have been standardised against the Phleum extract by comparative tests on the eyes of hay fever patients.

A measure of the patient's resistance during the experiments is obtained by observing the strength of pollen extract necessary to excite a conjunctival reaction. One drop of the diluted extract is instilled into the eye. The reaction obtained consists in a reddening of the caruncula and, to a lesser degree, of the palpebral conjunctiva, together with a slight injection of the vessels of the ocular conjunctiva and some lacrymation. The patient experiences a feeling of burning and itching. These signs reach a maximum in about five minutes, and a little later there may be a slight attack of sneezing. The reaction lasts as a rule about half an hour. The strength of the extract, which is just sufficient to give this reaction, is used to describe the resistance of the patient. The most sensitive patients examined gave before treatment a distinct reaction with a dilution containing only 4 units per c.c.; their resistance is described as 4; the least sensitive reacted to a strength of 70 units per c.c., or, in other words, had a resistance of 70. Normal individuals fail to react with the strongest extract (strength 20,000 units) and even resist the application of fresh pollen dust to the conjunctiva. Their resistance is therefore, by our scale, more than 20,000, but it is not infinite as a cubic centimetre of this extract injected beneath the skin of a normal man has been

[1] John Bostock: Medical and Chirurgical Transactions, vol. x., 1819, p. 161.
[2] C. H. Blackley: Experimental Researches on the Causes and Nature of Catarrhus Æstivus, London, 1873.
[3] W. P. Dunbar: Zur Ursache und spezifischen Heilung des Heufiebers, München, 1903.

Figure 1 Title page of Leonhard Noons original publication, Lancet 1911.

Fig. 3. Prima pagină a articolului lui L Noon despre imunoterapie în The Lancet, 1911.

Tabel I. Mecanisme propuse pentru modul de acţiune al ITS (după J. Ring).

- Inducerea de anticorpi specifici blocanţi IgG4
- Anticorpi blocanţi
- Reducerea sintezei IgE
- Blocarea receptorilor IgE la suprafaţa mastocitelor/bazofilelor
- Anticorpi anti-idiotip
- Inducerea sintezei de IgG şi IgA la nivelul mucoaselor
- Reducerea "eliberării" de mediatori
- Tahifilaxie
- Inducerea anergiei limfocitelor T
- Limfocitele T reg

În aceşti 100 de ani s-au utilizat tot mai mulţi alergeni pentru ITS: de la polen, utilizat iniţial, la alergenii din praful de casă, la animale (pisică, câine), mucegaiuri, veninuri de insecte (albine, viespi, furnici), alimente, medicamente.

Iniţial, pentru o lungă perioadă de timp, s-a lucrat cu extracte alergenice apoase, ulterior s-au introdus vaccinuri depot (modificate cu hidroxid de aluminiu). Alergenii au fost modificaţi pentru a reduce alergenicitatea şi a creşte imunogenicitatea; astfel s-au obţinut vaccinurile cu alergoide (concept dezvoltat în cursul anilor `70). Această modificare tehnologică a scăzut mult efectele secundare ale ITS. Pentru producerea alergoidelor s-au utilizat fie formaldehida (SUA), fie glutaraldehida (Europa) [5]. În viitor se vor evalua diferite vaccinuri alergice ce conţin alergeni recombinanţi, oligopeptide imunostimulatorii (CpG) etc.

Dezvoltarea ITS a dus şi la publicarea unei reviste medicale numită chiar Immunotherapy.

Recunoaşterea importanţei ITS s-a făcut şi prin conferirea Premiului NOON de către Academia Europeană de Alergolgologie şi Imunologie Clinică (EAACI) lui Alfred William Frankland (Fig. 4). Această onorare s-a

desfăşurat cu ocazia deschiderii Congresul Anual al EAACI de la Istanbul, 10-15 Iunie 2011. Frankland s-a alăturat lui J. Freeman în 1946 şi a publicat primul trial clinic controlat în ITS cu polen de graminee, împreună cu Rosa Augustin, în 1954 [9].

Fig. 4. AW Frankland la decernarea premiului NOON, Istanbul 2011.

Concluzii

În ultimii 100 de ani s-au făcut paşi importanţi în elucidarea mecanismului de producere a bolilor alergice. Paralel cu aceasta, s-a dezvoltat şi tratamentul specific sensibilizării alergice. Mulţi bolnavi au putut beneficia de efectele favorabile ale imunomodulării bolilor IgE-mediate. Viitorul va aduce noi vaccinuri cu alergeni, deoarece cercetarea este în plin avânt.

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