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CONTROVERSIES IN DERMATOLOGY

Biologic Therapies for Moderate to Severe Psoriasis Are Not Interchangeable☆

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Abstract Health care managers and hospital pharmacists are increasingly compelling prescribers to use medication substitutes. This policy becomes particularly evident when the agents are biologics with shared indications based on their assumed clinical equivalence and efficiency (cost-effectiveness), and in these cases the involvement of clinicians in decision making is often minimal or nonexistent. Lacking head-to-head clinical trials comparing various drugs, the prescriber can use indirect comparisons to define 2 or more agents as clinically equivalent therapeutic alternatives. This denomination of clinical equivalence does not imply that 2 such medications are truly therapeutically equivalent, or therapeutic equivalents, as this type of equivalence is defined by the absence of statistically significant differences between the drugs on all measures of effect in most patients, meaning that neither one is preferable to the other in different situations. Although real patients are not entirely comparable to those in clinical trials, the choice of a biologic agent to treat psoriasis is largely based on the findings of such trials. A recently published meta-analysis shows that not all the biologics currently available to treat moderate to severe psoriasis can be considered therapeutic equivalents, in spite of the authors' claim to the contrary; indeed, infliximab and etanercept can in no way be considered equivalent therapeutic alternatives based on the data provided. Biologics do display real differences with respect to efficacy at different time points and in the time required to onset of effect. In any case, therapeutic decisions should be made by an experienced clinician and tailored to each individual patient.

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Los tratamientos biológicos de la psoriasis moderada a grave no son alternativas terapéuticas equivalentes

Resumen Existe una tendencia creciente entre los gestores sanitarios y los farmacéuticos hospitalarios a insistir en la sustitución de fármacos, y en especial biológicos que comparten indicación terapéutica en función de una pretendida «equivalencia clínica» y consideraciones de eficiencia (eficacia/coste), a menudo con escasa o nula participación de los clínicos. Cuando no se dispone de ensayos clínicos comparativos *(head-to-head)* de diversos fármacos, se puede emplear el análisis comparativo indirecto para definir diferentes fármacos como «alternativas de tratamiento equivalentes». Que 2 fármacos se consideren «alternativas de tratamiento equivalentes» no demuestra que sean «equivalentes terapéuticos» o «terapéuticamente equivalentes»; para ello es preciso que en la mayoría de los pacientes no existan diferencias significativas (en todos los aspectos) que hagan que uno sea preferible al otro en determinadas situaciones. Aunque los pacientes en la vida real no sean totalmente comparables con los que participan en ensayos clínicos, la elección de un agente biológico en el tratamiento de la psoriasis viene determinada en gran medida por los resultados de los mismos. Empleando los datos de un reciente metaanálisis se comprueba que, en contra de la afirmación de sus autores, los tratamientos biológicos disponibles para la psoriasis moderada a grave no pueden considerarse alternativas terapéuticas equivalentes (en ningún caso por lo que respecta al par infliximab/etanercept). Existen diferencias reales en cuanto a eficacia en diferentes momentos y velocidad de inicio del efecto de los diferentes agentes biológicos disponibles, y en cualquier caso la decisión terapéutica debe ser tomada por un clínico experimentado de forma individualizada para cada paciente.

There is growing interest in assessing the relative effectiveness of alternative treatments that can—as in the case of biosimilars—offer cost savings and greater accessibility for patients, two objectives that should figure among the priorities of prescribing physicians. In the case of generic drugs, clinical equivalence is directly correlated with the presence of an identical active pharmaceutical ingredient (chemical) and proven pharmacological equivalence (bioavailability, etc.). In the case of biosimilars, however, there are obvious difficulties in extrapolating indications and determining interchangeability. Notwithstanding these difficulties, health care managers and hospital pharmacists are increasingly proposing the substitution of the prescribed biologics with other agents having the same indication. This is being justified by the assertion of a supposed clinical equivalence and considerations of efficiency (cost effectiveness).

Dermatologists and other specialists view this trend with growing concern, seeing it as incompatible with the need for individual treatment tailored to each patient. A further concern is that such substitutions may be based on assessments carried out by medical professionals lacking appropriate clinical competence in this area and that the analyses used are sometimes invalidated by conceptual or methodological errors. The problem is illustrated by a recent article that concluded, on the basis of a meta-analysis, that all currently available biologic agents for the treatment of psoriasis are ''clinically equivalent'' because the 95% CI of the absolute risk differences for achieving a greater than 75% improvement over baseline on the Psoriasis Area and Severity Index (a PASI 75 response) did not reach the ''threshold for clinical relevance'' of 25% fixed by the authors.[1]

In the absence of head-to-head comparative trials, the comparative effectiveness of different drugs can only be inferred indirectly through meta-analysis of data from the available clinical trials.

In order to define 2 or more agents as clinically equivalent therapeutic alternatives we must first define the concept of clinical relevance. However, a certain degree of confusion exists between this concept (which determines the efficacy outcome of clinical importance that should be assessed—for example, patient survival, a decrease in blood pressure, clearing of psoriasis, a specific PASI score, or a predefined percentage of reduction over baseline PASI) and other concepts including the following:

Absolute risk reduction (also called risk difference), which is the difference between the percentage of patients in the intervention group and the control group who achieved the outcome measure at a predefined point in the trial.

Effect size, which quantifies the magnitude of the difference between 2 or more groups in a clinical trial, and which is generally expressed either as an odds ratio (OR) or the number needed to treat to achieve the efficacy outcome measure (NNT). The NNT is the reciprocal of the absolute risk reduction.

The delta value, or difference in response rates between the 2 groups being compared. This value determines the null hypothesis (no difference or inferiority, etc.) making it possible to calculate the size of the sample required in a clinical trial for a determined probability of a type I or α error—that is, rejection of a true null hypothesis or a false positive—or a type II or β error—that is, failure to reject a false null hypothesis or a false negative.