Is Alpha-1 antitrypsin augmentation therapy an essential medicine?

Alpha-1 Antitrypsin Deficiency

Alpha-1 Antitrypsin Deficiency (AATD)is a genetic condition that can cause lung and liver damage . The genetics and pathology of the disease have been extensively reviewed (1). The protein Alpha-1 antitrypsin (AAT) is encoded by the SERPINA1 gene and mutations in this gene cause deficiency and accumulation of abnormal protein in the liver. The normal allele M results in the normal genotype PiMM, with common deficiency genotypes being PiZZ and PiSZ. The PiZZ genotype results in the most severe form of the disease. The only available treatment is by augmentation of the missing/defective protein through administration of AAT concentrate purified from human plasma or recombinant sources (2) . This therapy has been available for decades but randomised clinical trials examining its efficacy have been published only recently. Early regulatory assessment based on biochemical and pharmacokinetic studies led to approval in a number of countries, with more recent approvals being based on randomised clinical trials (RCTs) for efficacy (3) but access to the therapy has been limited in many countries, with only seven European Union states providing reimbursed full access to the product (4).

The concept of *essential* and *crucial* medicines

In 1975, the then Director of the World Health Organisation (WHO) Halfdan Mahler, addressing the World Health Assembly, warned of the need to ensure access of the most essential drugs at an affordable price. In 1977 this was succeeded by the WHO's publication of a list of essential drugs, then defined as drugs which are "basic, indispensable and necessary for the health of populations". Successive editions of this list, renamed the Essential Medicines List (EML), together with a separate list for of essential medicines for children (EMLc), have been published. The most recent EML/EMLc (the List) was published in July 2023 (5). The choice of essential medicines follows applications which are considered for inclusion in the List by a WHO Expert Committee on Selection and use of Essential Medicines. The WHO's most recent definition of essential medicines states that:

"Essential medicines are those that satisfy the priority health care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness. They are intended to be available in

functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford."

Since the WHO's first edition of the List, 137 countries have published their own lists of essential medicines, which do not always reflect the EML. The EML has been shown to influence reimbursement and access to medicines, particularly in low and middle income countries (LMIC) (6), although the global availability of essential medicines is low.

In addition to alluding to public health and relevance and disease prevalence, the WHO's definition refers to cost-effectiveness. In assessing cost-effectiveness, the WHO draws on economic data which should be submitted by applications for inclusion in the EML, despite that the majority of such applications are incomplete (7). Notably, applications from the commercial sector had the lowest rate of provision of economic data, although this did not affect the probability of inclusion in the List. These considerations of cost-effectiveness are of importance in the assessment of expensive medicines, and the particular case of orphan medicines, which are by definition restricted to small patient groups outside the main priorities of population health, is especially challenging . These medicines, which include, but are not restricted to, treatments for rare, chronic diseases such as AATD, are generally expensive and outside the budgetary reach of many Low and Middle Income Countries (LMIC) which draw on the List to establish their National Formulary (8). In 2005, the then Director for Essential Medicines of the WHO suggested that for orphan diseases not constituting a global public health priority, there was no justification for their treatments to be listed in the list (9). Included in this assessment were products for rare, chronic, diseases, such as Haemophilia A and B. The treatments for these latter diseases had been withdrawn from the List but were reinstated following an outcry from patient organisations. It was suggested that the provision of of such medicines should be through donation programs or private purchase, but not through the public health system. The WHO's position has evolved over the successive editions of the List, with 1.9% of listed medicines being classified as orphan drugs in 1977 rising to 14.6% in 2021, although the average interval between regulatory approval and inclusion in the List was 13.5 years, reflecting the WHO's additional assessment of accrued, real-world effectiveness (10). The List now includes expensive drugs for the treatment of rare cancers, reflecting the current selection principles that price should not impede inclusion in the List if the other criteria are fulfilled (8). It has been suggested that cost-effectiveness should be excluded from the WHO's consideration (11), and replaced by processes for financing and procuring essential medicines for resource-limited countries (12). A process of progressive realisation has also been proposed, whereby treatments for rare disorders are ranked on the basis of comparative cost-effectiveness and

resources allocated as they become available, until all patient needs are met (13). Such an approach needs to factor in the consequences of postponement of treatment in certain chronic diseases, such as AATD, where disease progression may lead to irreversible effects, as outlined below.

Another mechanism for assisting decision making in medicine procurement is Health Technology Assessment (HTA), which includes an aggregate of analytical tools, including cost-effectiveness analysis (CEA), and is used widely to assess the suitability of individual medicines for public reimbursement. Unlike the population health emphasis of the EML, HTA is focussed on the individual medicine's capacity to satisfy health funders that the medicine provides value for money relative to pre-defined criteria for cost-effectiveness (14). These criteria vary between countries, and involve modelling which is not always available, especially in LMIC. The methodologies have been developed and implemented to evaluate treatments for common conditions, and treatments for rare, chronic disorders often fail to meet conventional criteria for cost-effectiveness using standard CEA methods (15). Some of the inputs included in the modelling present problems when assessing patients with rare, chronic diseases. These include the use of health utility metrics to assess the added benefits of treatments, which can be affected by the "disability paradox" frequently encountered in these patients (16–18). Despite these limitations, many orphan drugs not conforming to conventional CEA criteria are subsidised publicly. Alternative and supplemental frameworks for the assessment of rare, chronic disease treatments have been proposed (19,20).

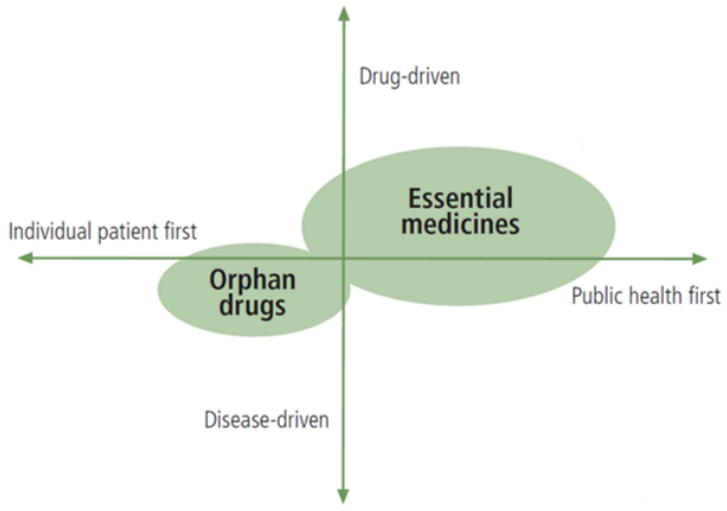

Figure 1 *Priorities in bringing important drugs to patients: two dimensions.*

From Stolk et al (2006) Drug-driven" refers to more emphasis on the drug compound for decision- making (e.g. cost–effectiveness, evidence base). "Disease-driven" refers to more emphasis on the characteristics of the disease in the decision-making process.

In summary, there is a level of tension between the provision of essential medicines on a population health basis and the funding of medicines for orphan conditions such as rare, chronic, diseases (**Fig 1** from (11)). Despite this, the inclusion of these medicines has increased steadily in the WHO's List

over the years since its inception. Health Technology Assessments for individual medicines have also not proven to be a significant impediment to access these therapies, despite often not meeting CEA criteria. These developments have evolved as processes such as the EML and HTA have adapted their criteria to include wider use of effectiveness data from real-world experience and have developed special provisions for expensive and specialised drugs.

The European Union (EU), through its European Medicines Agency (E MA), has now published its own list of *critical* medicines. The EU specifies its list a tool in its efforts to secure the supply and prevent shortages of critical medicines. The EU considers a medicine to be critical if it is used in serious diseases and cannot be replaced by other medicines. Importantly, to be included, it needs to be considered as critical in more than one third of EU countries. The first (2023) edition of the EU list is extracted from a review of 600 active substances included in the critical list of six EU members. The EU's methodology for assigning "criticality" is available (21). Criticality is based on two criteria:

1. The therapeutic indication for which the medicine is used. High, medium and low risk levels are assigned. High risk indications are specified as having *"very serious implications for the health of individual patients or public health"*, requiring treatment of *"general life-threatening acute conditions, specific life-threatening conditions or irreversibly progressive conditions."*
2. The availability of appropriate alternatives.

There are differences in emphasis between the WHO's EML and the EU's list of critical medicines. The WHO's allusion to prevalence and public health relevance points to the WHO's priority in achieving outcomes for LMIC, for whom low prevalence rare diseases are less of a priority than large public health issues such as vaccination, tropical disease such as malaria etc. However, the EML does include medicines for rare, chronic diseases such as haemophilia and primary immune deficiency, as well as medicines for rare cancers (8). The EU's list specifies the individual patient, as well as the public health, and has no allusion to disease prevalence and cost-effectiveness. It too includes medicines for rare chronic conditions.

Neither of these lists includes AAT concentrate. While the exclusion of this therapy from the EML might be partially ascribed to the WHO'S priorities, its exclusion from a list developed by the EMA, which has approved brands of the product for the whole of the EU after full evaluation for safety and efficacy, is less easy to understand. Both criteria specified above seem to be satisfied in regard to this therapy. In addition, the EU is committed to improving the lot of rare disease patients, such as those with AATD. The Critical List's focus on avoiding shortage is also

highly relevant to plasma-derived medicines such as AAT concentrate, and will be discussed further below.

The claims of AAT concentrate to the EU's list of crucial medicines

Uncertainty regarding its efficacy in ameliorating AATD has dogged the use of AAT concentrate for many years, and has led one Cochrane Review to consistently advise against the therapy (22). The apparent lack of effect of AAT augmentation therapy on indicators of respiratory function, particularly spirometric indicators, including Forced Expiratory Volume (FEV1), as well as a lack of mortality data, have contributed to this. The large number of patients needed to demonstrate a change in FEV1 (23) led the United States Food and Drug Administration's (FDA) Blood Products Advisory Committee (BPAC) to accept serial lung density measurements by high-resolution computed topography (HRCT) as a clinically meaningful end-point to assess augmentation therapy, requiring fewer patients to demonstrate power in a clinical trial. More recent studies, reviewed in (1), and a real-world observational study interrogating data from patient registries, indicate a plateauing of FEV1 decline in AAT deficient patients as they reach fifty years of age (2). This is the age group contributing mostly to clinical trials, suggesting that FEV1 may not be a suitable indicator for monitoring the efficacy of augmentation therapy. In this real-world study, in AATD patients at Grade 2 of the COPD Gold Classification FEV1 decline was slowed compared to untreated patients. Such patients whose symptoms are mild at diagnosis are not administered AAT concentrate (24) until their pulmonary function deteriorates to a stable low level unresponsive to augmentation therapy. The US Food and Drug Administration (FDA) and the EMA have now accepted that other endpoints, and in particular the measurement of lung density in two RCTs, reviewed in (25), may provide the basis of regulatory approval for the marketing of brands of AAT concentrate in the USA and the European Union. Lung density has also been shown to correlate with clinical outcomes, including mortality and Quality of Life (26,27). Augmentation therapy has also been shown to improve survival significantly in the same large real-world study (2). It has been suggested that the results of these studies render the inclusion of a placebo arm in trials of AAT concentrate ethically questionable (2), as is also pointed out by the European Respiratory Society (4).

These more recent findings suggest that the Cochrane Review's most recent assessment, which was published in 2016, requires revision. We would encourage the Collaboration to produce another updated Review on AAT augmentation therapy, considering the findings, touched upon in this Perspective, which have enhanced the position of augmentation therapy since 2016. In

particular, the limitations of FEV1 measurement and the damage wrought by treatment delay merit attention. Given the ethical dubiousness of further placebo-controlled trials, real-world evidence should be used to widen the evidence-base of augmentation therapy. We note that the use of such evidence is now accepted by bodies charged with the assessment of health care interventions (28) and that the Cochrane Collaboration has also noted the convergence of such evidence with that generated from randomised trials (29).

The use of the EU's Critical Medicines List in securing supply and preventing shortages has particular relevance for plasma-derived medicines such as AAT, given the fragility of the supply chain of these products due to the particular features of the plasma raw material. Europe's supply of plasma products is currently dependant on a surplus of such products produced by the USA in excess of the market needs in that country (30). This dependence led to substantial shortages when plasma collection in the United States was affected by the Covid-19 pandemic (31,32). Protectionist measures have also been proposed by US legislators, aimed at restricting the volume of plasma available for the exports of products to Europe (33). Measures to secure the supply of critical plasma products are essential for ensuring the welfare of European patients dependant on these therapies.

In the interim, the wider evidence base for augmentation therapy, in tandem with the considerations around shortages outlined above, should contribute to a revision in the EU's critical medicines list so that succeeding versions include AAT concentrate. It is to be hoped that this inclusion, enhancing the status of AAT concentrate within the European Union, would contribute to an expansion in access to this therapy within the EU. Organisations advocating for patients with AATD, including the organisation of the current authors, will continue to engage in dialogue with the EMA with the aim of achieving this outcome.

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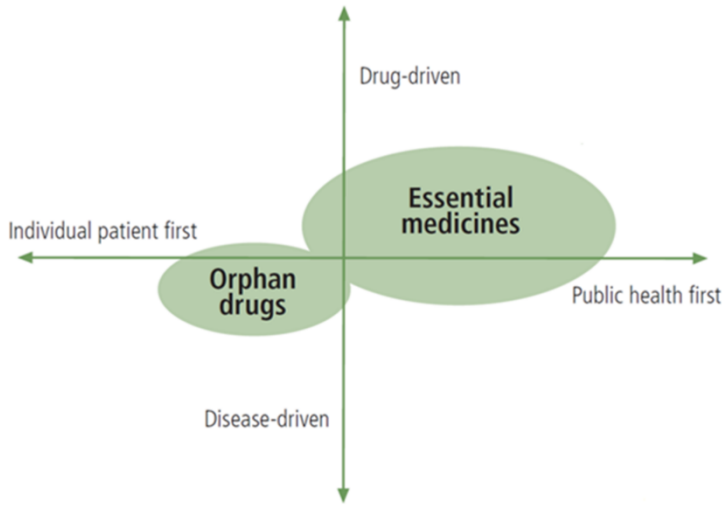

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