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EDITORIAL

Restricting the number of drug options that can be used to treat a disease results in unsatisfactory outcomes for patients, prescribers and payers alike.

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EDITORIAL

Developing new drugs is extremely expensive often costing upwards of a billion dollars to bring a drug to market[1]. This is driven by the studies required to demonstrate the safety of the drug and bears little relation to the cost of manufacture. Demonstration of efficacy generally requires much smaller numbers. The level of safety required is, quite rightly, stringent, and is to give confidence that unexpected side effects are unlikely to be found when the drug is released for use in the general population. If a lower level of safety was accepted, then drugs could be considerably cheaper, but at a risk. However, the study patients are selected, usually for having active disease and few other conditions to complicate response. It is estimated that only about 30% of patients seen in clinic are suitable for any particular study[2] so we can't know for sure what will happen when it is available to the other 70%. This is a weakness of the evidence base[3].

Drugs are licensed on a risk benefit analysis by the drug regulators eg the MHRA. More recently, driven by the expense of new drugs, in the UK, before they can be used they have been required to show cost effectiveness through a National Institute for Clinical Excellence (NICE) assessment where the cost of the improvement in quality of life needs to hit an acceptable threshold[4]. There is often press and political interest in these approvals. The aim of NICE is to ensure value for money and equality of access to drugs, abolishing postcode prescribing where different geographical areas have different access to drugs. However, the Clinical Commissioning Groups (CCGs) who pay for the drugs, may have their own interpretation of guidelines, and NICE approvals, which apply in their area. An example of this was a restriction on the number of higher cost drugs (HCDs Biologics and JAKi) that could be tried for RA by a substantial number of CCGs in England[5,6].

At a session of the BSR annual meeting in 2019 discussing what Rheumatologists do when the patient in front of them doesn't fit the guideline for a treatment that they think will be effective, it became apparent that a substantial number of rheumatology services were restricted by their CCGs[7]. Those of us from unrestricted areas were surprised and could not understand the logic for this restriction. The main reason discussed was that these drugs had not been shown to be cost-effective at higher choice points. That was, of course, true but only because the studies had not been done, another weakness of the evidence base[3]. Lack of evidence is not evidence of lack of effect.

With a joint working agreement with Gilead Pharmaceuticals[8], we then embarked on a series of studies to explore the situation and the effects of the restrictions. Our purpose was to explore the current situation with regard to restrictions by surveying the CCG guidance; define patient response to late choice drugs by reviewing the experience of our unrestricted service; to understand the impact of the restrictions on prescribers through a survey and to explore this qualitatively with semi-structured interviews; and lastly we sought to understand the patient perspective with interviews with patients who had used many therapies.

We initiated a review of the guidance of all of the CCGs in England[6]. This review which was conducted between June and October 2020 showed that just under half of them restricted the number of biologics or targeted synthetic drugs (65/134). The restriction was: 10 CCGs restricted to 6 choices; 49 restricted to 4 choices and 9 restricted to 3 choices. This was similar to another survey conducted by "freedom of information" requests done about the same time[5]. There were subtle differences with regard to whether it mattered if the failure was a toxicity and for the different modes of action. It was therefore clear that a substantial minority of CCGs were seeking to limit the number of drugs that could be tried. While not stated it seemed clear that the intention was to reduce costs on the basis that cost effectiveness had not been shown at that choice point and an assumption that the response rates would be lower with each subsequent drug. The concept of difficult to treat, or resistant disease.

There are little data on the response rates after increasing numbers of failed treatments. Phase 3 and 4 studies often include a group with treatment failures but usually this is restricted to a small number[9], presumably on the same reasoning of the CCGs, that these patients may be resistant to treatment and may not respond to the test drug. Observational studies are susceptible to bias being dependent on clinical decisions that are made for clinical reasons[10]. However, the alternative of randomising patients at each choice point would be very complicated and would take a considerable amount of time going forward. We therefore decided to review the experience of patients in our unrestricted service requiring four or more HCDs looking primarily at response rates and duration of treatments. Forty-nine patients were found out of 2,648 RA patients registered with us, which represents less than 2% of our RA population. The most drugs used by an individual at that time was 9. Our results showed response rates between 50 and 55% for 4th 5th and 6th choice drugs[11]. Patients were, therefore, likely to respond to late choice drugs. Numbers were small above 6th choice making it difficult to draw conclusions, but the patient on their 9th choice was a responder. Only 4 of the patients had given up trying to find further treatment, 2 for toxicity reasons and 2 where they were considered not to have sufficient uncontrolled inflammation to justify another treatment. Primary failures of treatment were more likely to fail subsequent treatments than secondary failures and changing mode of action was more likely to work than repeating the previous failure. In terms of duration of treatment, a lot of these patients were getting a few years out of each drug, yet still responding to the next one. In our service, then, it is worth continuing to try further drugs even after many failures.

We were interested in the effect of the restrictions on prescribers. We therefore conducted a national survey of prescribers seeking information on any restrictions to prescribing in their service and the effects this had on their prescribing[12]. The prescribers in restricted areas found the restrictions frustrating and that they were unable to do their best for all of the patients. The safety valve of the individual funding request (IFR) was regarded as ineffective as cases were very likely not to be individual enough as if there was a cohort of patients requiring the treatment, then the IFR was not appropriate and a change to the guideline was

required. Most prescribers had given up even applying. They also said that they were likely to persist with partially effective therapy, rather than trying to find something better, in order to avoid running out of options. This clearly would mean that the CCG were paying full price for partial effect, the antithesis of their objective.

We explored this further with a qualitative study using semi-structured interviews with 6 prescribers from restricted areas[13]. They confirmed the unsatisfactory nature of their service, one actually becoming upset when faced with and forced to think about the service that he was being constrained to offer. The hanging on to partially effective treatments sometimes started pre biologic. It is important to remember that RA is a disease where permanent damage is related to the area under the curve on an inflammation / time graph where early control of the inflammation is essential for long term good outcomes[13]. The one area of optimism from these interviews was that services were sometimes able to minimise the effect of the restrictions by negotiating a pathway with the CCG which allowed more use.

Finally, we were interested to get a patient perspective from our patients who had had 4 or more HCDs. What would they have thought if they had not been allowed to try the later choice drugs? We did this with semi-structured interviews with 5 of our multiple user patients who volunteered to be interviewed[12]. The interviews were remarkably consistent with patients making it clear that running out of options was the worst thing that could happen. They were realistic in that they understood that there was no guarantee of response, but they needed to "travel hopefully". They used quite florid language to describe this with phrases such as "the end", "my life would be over" or "may as well be dead". It seems that the prescribers were responding to this fear among the patients of having no options, by delaying changes in the drugs and spinning things out, even though that is not medically sound.

Our conclusions are that restricting drugs by number does not make any sense. Clinical Commissioning Groups end up spending the same amount of money, as patients remain on treatment, but getting a poorer response. Clinicians should be incentivised to cycle through the drugs at an appropriate rate looking for the optimal treatment effect. The drug that gives that optimal effect will, by definition, be the treatment that has the greatest cost effectiveness.

Conflict of Interest:

None

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