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REVIEW ARTICLE
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Considerations for dosing immunoglobulin in obese patients

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Summary

Obesity is a very common condition; however, the effect of excess body weight on the appropriate dose of immunoglobulin has not been defined empirically. The proposed pharmacokinetic differences between lean and obese patients and the opportunity to reduce costs has led to the proposition that obese patients should receive proportionally lower doses of immunoglobulin once a certain threshold is reached. Here the theoretical factors which could affect dosing in obese patients are considered alongside the available empirical evidence. The available evidence indicates that obesity may affect the pharmacokinetics of immunoglobulin; however, the effect is likely to be too small to have a clinically important effect on dosing. Wide interpatient individuality and highly variable clinical need mean that obesity should not play a major factor in dosing considerations. However, patients who are obese are more likely to have multiple cardiovascular risk factors and their weight indicates a large dose. This puts these patients at a higher risk of adverse reactions, and therefore caution is advised.

Keywords: dosing, immunoglobulin, IVIg, obesity, primary immunodeficiency

Introduction

It is recommended to dose immunoglobulin (Ig) for both replacement and autoimmune indications with reference to actual body weight [1,2]; however, clinicians have long queried whether this is the optimal dosing approach for all patients [3,4]. In general, how dosing can be optimized to maximize efficacy while minimizing cost and the risk of adverse events is an important question. In this short review the focus will be on the challenges the obese patient population presents and how dosing can be optimized in this group.

Optimum dosing of immunoglobulin remains a hotly debated topic in general for both replacement and autoimmune indications [5,6], so tackling this topic in a subset of patients who are not well represented in research [7,8] is challenging. Zuckerman *et al.* [9] advocate that obese patients should be considered as a special population and included as standard in all clinical trials, as well as introducing the requirement to record body mass index (BMI) in all post-authorization safety studies (PASS). This idea, although currently peripheral, is likely to become more accepted as obese people represent a significant and growing proportion of the global population, and this is particularly pronounced in areas of high immunoglobulin (Ig) use. The World Health Organization (WHO) estimated that more than 20% of people were obese in Europe in 2010 [10], and the Centre for Disease Control published figures showing that >36% of people in the United States were obese in 2014 [11].

The WHO defines obesity as a body mass index of above 30 kg/m^2 and overweight as >25 kg/m^2 [12]. In non-athletes BMI remains a strong indicator of body fat composition and health risk while also being a readily available parameter, and therefore that is how the term obesity is used here. The usefulness of BMI has been criticized severely within the sporting world due to the insensitivity to muscle and bone mass [13]; however, for the largely sedentary patient population receiving immunoglobulin it is appropriate.

Dosing adaptations are made routinely to take into consideration factors which affect drug metabolism and excretion (e.g. hepatic and renal function); however, very little consideration is given to obesity, which has the potential to affect all aspects of drug pharmacokinetics and has a much higher prevalence.

Current dosing practice by clinical immunologists in primary immunodeficiency (PID) is largely unaffected by obesity and generally reflects guidelines with a standard starting dose of 0·4–0·8 g/kg/month alongside evidence-based alterations made based on clinical factors (e.g. presence of bronchiectasis [14]). Further optimization is then undertaken in the maintenance phase based largely on clinical response, but also on laboratory parameters, tolerability and patient preference. Whether the presence of obesity specifically affects these general factors remains a topic of debate.

The situation in higher-dose indications is slightly different, where significant emphasis is put on reducing the starting dose from the (largely arbitrary) 2 g/kg starting point and also the use of maximum total doses due to safety considerations. This is important, as although the original use of Ig was in PID indications, such as common variable immunodeficiency disorder (CVID) and X-linked agammaglobulinaemia (XLA), these now represent a fraction of the overall need, with neurological and haematological conditions playing an increasing role. Most patients receiving Ig for neurological conditions (e.g. the peripheral neuropathies; multi-focal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP)) are immunocompetent and often receive much larger doses than replacement (PID) patients. This means that following Ig administration the IgG levels in a peripheral neuropathy patient may be very high, which will affect the pharmacokinetics and safety considerations in these patients. Use in secondary immunodeficiency (particularly iatrogenic) has become more important in recent years [15], but the dosing and risks in these patients are similar to PID patients, with the exception of myeloma, where a very high baseline IgG plasma concentration may be present and therefore hyperviscosity must be considered.

Theoretical factors which may influence the pharmacokinetics of IgG in obese patients

There is a reasonable body of literature investigating the empirical effects of obesity on the pharmacokinetics of small molecule drugs allowing some general principles to emerge, but consensus does not yet exist [16–18]. The situation in immunoglobulin administration is more difficult due to the paucity of data and the unique characteristics of Ig, therefore this section is a summary of established physiological differences between lean and obese patients which may influence the pharmacokinetics and therefore dosing of immunoglobulin (see also Fig. 1).

Hydrophilicity

Immunoglobulin G (IgG) is a relatively polar molecule with a small volume of distribution (V_D), which generally means that the drug molecules accumulate preferentially in aqueous compartments, e.g. plasma [19]. Therefore, penetration of the active ingredient into adipose tissue/lipophilic environments has been postulated to be poor, which could result in a higher plasma concentration in obese patients despite the same dose/kg. Of course, IgG distribution is not simply the function of a partition coefficient *in vivo*, and IgG can be particularly influenced by active transport and inflammation [20–22]. For monoclonal antibodies the distribution is altered specifically by binding to the target antigen; however, this is not the case for polyvalent normal human immunoglobulin [23].

Blood volume

Perfusion of adipose tissue relative to lean tissue is known to be poor, which may exacerbate the partition effect discussed above through a reduced opportunity for a plasma concentrated drug to access adipose tissue [24]. Likely to be of more consequence is the fact that total blood volume relative to actual body weight is reduced in obese patients compared with lean patients (50 *versus* 75 ml/kg) [25]. The effect of lower ml/kg blood volume on protein drug pharmacokinetics was demonstrated well by Wang *et al.* [26] in laboratory animals who received the same g/kg dose, but the obese animals exhibited higher plasma drug concentrations. Of relevance to the route of adminstration was that this applied only to intravenous (i.v.) dosing and was not replicated when the animals were dosed by the subcutaneous (sc.) route.

Neonatal Fc receptor (FcRn) recycling

FcRn; which protects IgG from lysosomal degradation, facilitates creation of an intracellular protein reservoir and subsequently recycles IgG back into the circulation, is responsible for the long half-life of IgG *in vivo* [27]. It is distributed widely throughout the body, although there is some evidence that expression in adipose tissue is lower than in other tissues (e.g. skin and muscle) [28,29], which could result in a lower capability of obese patients to recycle IgG.

Clearance

Clearance of protein drugs may not be linear with body weight. It is hypothesized that although clearance increases with body weight, at higher weights the increase may be non-linear [30], which would mean that heavier patients would have a slightly reduced rate of clearance per kg body weight which could result in an extended IgG half-life. This effect comes with some significant caveats, which are that it would apply similarly to those of high body weights due to height, muscle mass or obesity and also that it is extrapolated from general protein drug behaviour rather than from the characteristics of IgG.

Obese patients have chronically enhanced inflammation

Adipose tissue is not simply an energy storage compartment; it is a metabolically and immunologically active

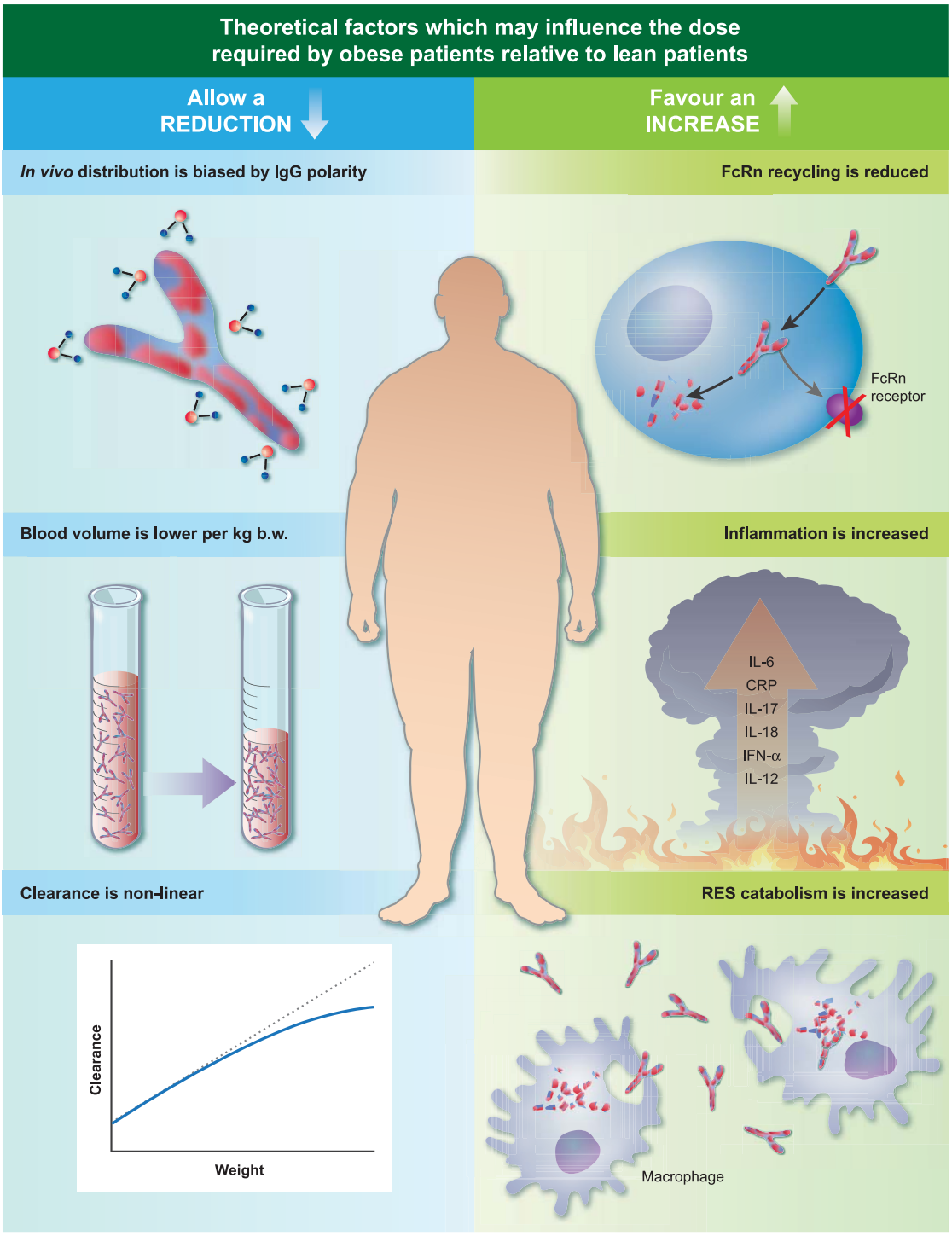

Fig. 1. Theoretical factors which may affect immunoglobulin (Ig) pharmacokinetics in obese patients. IgG is a polar molecule, and therefore a preference for the aqueous spaces (e.g. blood) would be accentuated in obese patients. This preference may be additionally pronounced because obese patients have a proportionally (per kg body weight (b.w.)) lower blood volume compared to lean patients. Furthermore, protein drug clearance is proportionally lower as weight increases, which may contribute to an extended half-life for Ig. The chronic inflammatory state seen in obese patients may necessitate a higher dose to control symptoms, as would an increase in Ig catabolism and reduced recycling due to a shorter $t_{1/2}$.

tissue [31]. In normal adipose tissue (lean patients), pro- and anti-inflammatory adipokines balance to create metabolic and immunological homeostasis. However, in obesity the balance tips to production of excess chemokine (C-C motif) ligand 2 (CCL2), interleukin (IL)-1β, IL-6, IL-8, IL-12, IL-17, IL-18, tumour necrosis factor (TNF)-α,

interferon (IFN)-γ and C-reactive protein (CRP), which are transported to the systemic circulation and precipitate a chronic inflammatory state which causes, predisposes to and exacerbates conditions such as type 2 diabetes, cancer and cardiovascular diseases [31–37]. This is part of the metabolic syndrome found in obesity which is characterized by high waist circumference, raised blood pressure, raised triglycerides, reduced high-density lipoprotein cholesterol and raised blood glucose [38]. Although the metabolic syndrome is simply a collection of risk factors, the associated inflammatory state exacerbates immune dysregulation, including pathogenic antibody production by functionally altered B cells [39], and may increase the functional requirement for IgG replacement in obese patients suffering from PIDs. In the obese state increased levels of activated and effector proinflammatory $CD4^+$ and $CD8^+$ T cells and reduced levels of immunoregulatory T cells (T_{regs}) are found in visceral adipose and contribute to immune dysregulation [40,41]. It is clear that in PID the autoimmune and inflammatory complications are driven by the underlying genetic/molecular defects particular to the pathophysiology of each patient (e.g. cytotoxic T lymphocyte antigen (CTLA)-4 deficiency); however, it is plausible that additional obesity mediated immune dysregulation, which is well documented, may worsen the prognosis or exacerbate symptoms. Indicators that this is likely can be seen in the detrimental effect obesity has on response to vaccines [42] and increased mortality following infection with influenza [31,43]. Interestingly, there is a mortality advantage of obesity in sepsis which is hypothesized to be due primarily to the haemodynamic benefit of the hypertensive state and protection from a catabolism-mediated nutritional deficit; however, there was also a role for the distinct immunological status of the obese patient [44]. It would therefore be interesting to know if these effects have an impact on any of the indications for which Ig is prescribed, but particularly in primary immunodeficiencies such as CVID, where proliferative, inflammatory and autoimmune complications cause significant morbidity [45] and can prove a more difficult challenge for treating physicians than classical infectious complications [46]. The consequence of these combined effects may be the need for a greater than proportional increase in dose in the obese PID patient to ensure that both the underlying condition and the obesity-mediated immune dysregulatory exacerbation and are attended to sufficiently.

Catabolism of IgG

In concert with the increased inflammatory propensity of the obese patient discussed above, the population of activated macrophages is also expanded significantly in excess adipose tissue [47]. As the primary elimination mechanism of IgG molecules is via the reticuloendothelial system [48], this is likely to contribute to increased catabolism of IgG and a reduced half-life in comparison with lean patients.

Established physiological differences between lean and obese patients are described above, although some amelioration of opposing factors is likely and the cumulative impact of these individual factors on Ig pharmacokinetics, and therefore dosing, remains theoretical.

Cost and safety

The particular physiology of obese patients contributes to theoretical factors which could mean that either an increase or a decrease in dose is warranted. However, pharmacokinetic factors are not the only considerations when formulating the most appropriate treatment for any group of patients or in particular any one individual.

Ig is a high-cost medicine, and in many indications where it is utilized successfully dosing studies have not been performed; e.g. the 2 g/kg starting dose in some autoimmune indications may not be fully evidence-based. There is now some evidence which supports the reduction of Ig doses from the starting dose to a lower maintenance dose in immunomodulatory conditions [49]. Observational studies across both lean and obese patients in CIDP indicate that although the dose range and frequency used in maintenance is wide, 1 g/kg/month is sufficient for stability [50]. It should be noted, however, that very high doses may be necessary in some acute conditions e.g. 3 g/kg over 2–5 days in divided doses for toxic epidermal necrolysis [51]. Under these circumstances, where a very high dose is necessary, safety is the primary concern.

The management of chronic autoimmune conditions requires that responsiveness to Ig therapy is first demonstrated followed by a dose appropriate to maintain that response. This therefore requires that a sufficiently high initial dose is used to ensure that all potential responders are detected. Following this, it is appropriate that clinicians titrate the starting dose so that it strikes the right balance of cost and effectiveness in maintenance therapy. This question is driven by a twofold desire to reduce health system expenditure and optimize patient care, and has been successful in achieving this in individual patients [5,14,52–54]. The desire by some budget holders to solely reduce costs exerts a blind downward pressure on the dose used. However, the balance between safety and effectiveness is much more subtle, and requires the lowest possible dose which achieves the best possible outcome for the patient during both the short and long term. It is important to note that costs to a health system are much more related to the maintenance dose and the long-term wellbeing of the patient. The best way to ensure that both of these are optimized is through an individualized dosing regimen.

The question of drug safety is particularly relevant for obese patients due to the larger doses used and the generally higher risk of adverse reactions, which is associated with

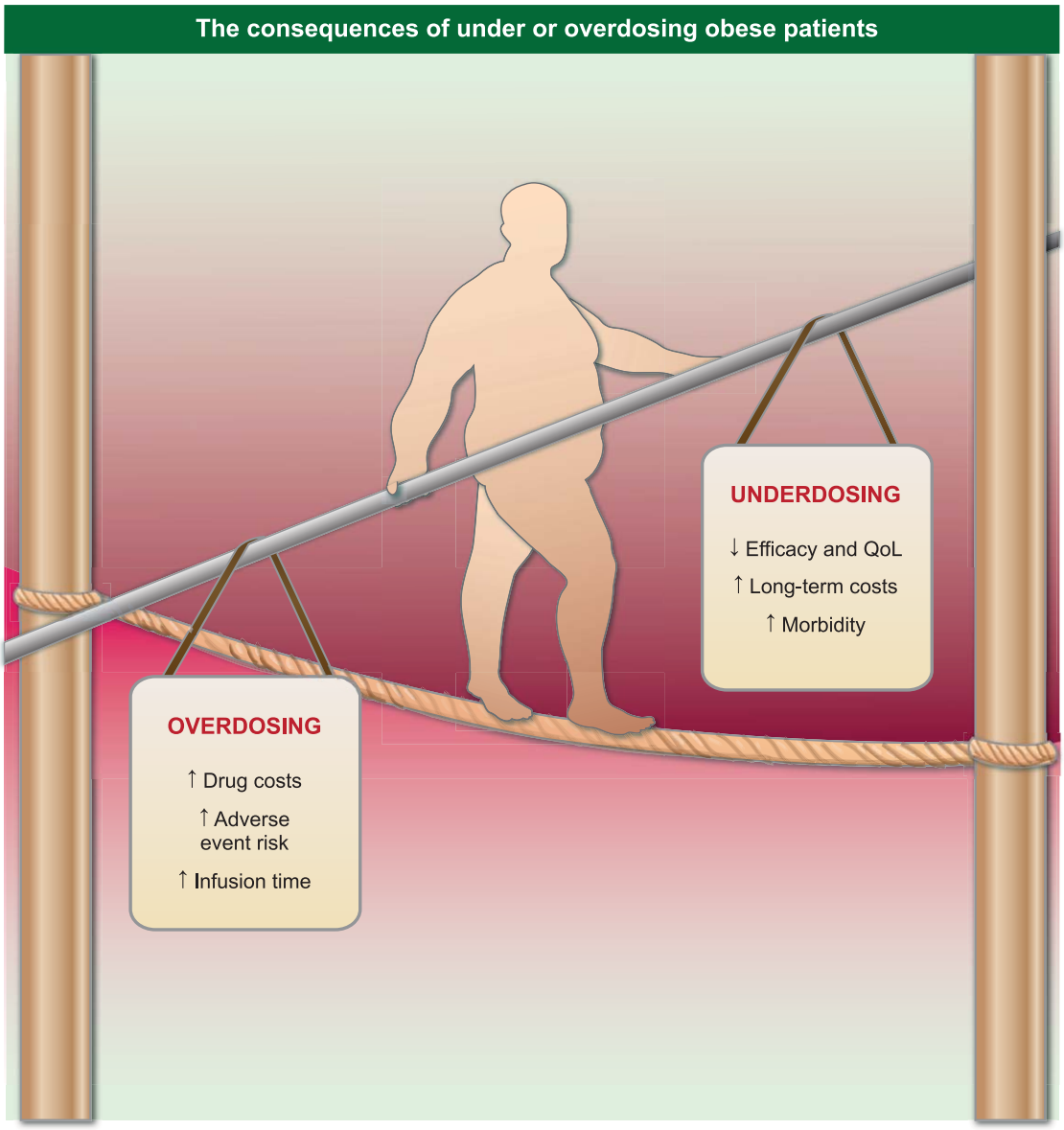

Fig. 2. The consequences of under- or overdosing can be felt by both the treating clinicians and the health system, but will primarily affect the patient. General dose recommendations are useful to the treating physician; however, the balance necessary for each patient must be made on a individual basis where all factors can be considered. QoL: Quality of life.

obesity and other co-morbidities common in this population (e.g. diabetes mellitus, hypertension, history of vascular disease). It must also be remembered that, irrespective of weight, the question of safety is likely to be much more pressing in the patient groups receiving larger doses, i.e. in general those patients being treated with Ig for immunomodulatory reasons with doses of 1–2 g/kg. Some practical mitigation steps should be followed where risk factors are present. These include adequate hydration of the patient prior to the infusion, maintaining the appropriate infusion rate, deferring the infusion if the patient has an active infection, dividing very large doses and, in cases where a particular risk is apparent, blood viscosity can be monitored or weight loss advised. While cutting costs and reducing risk are important arguments for short-term impact, many of the conditions where Ig is used are chronic diseases with high levels of long-term morbidity and mortality. The balance which must be struck is illustrated in Fig. 2, and should be considered in the context of the primary purpose of giving any medicine which is to improve the quality and duration of patients' lives. An important goal of Ig administration is to reduce the risk of lesions to physical structures which are irreversible and refractory to treatment (e.g.

bronchiectasis in CVID [55] and permanent axonal damage in MMN [56]), therefore highlighting the necessity of optimal dosing in the long term.

Although safety is always paramount, patient preference may also be important here as larger doses result in longer infusion times or the use of higher infusion rates. The latter, particularly, may reduce tolerability (e.g. increased levels of transient, reversible side effects such as chills or headache) and may necessitate divided doses, which are inconvenient and can limit options in the use of alternative routes of administration (e.g. s.c. Ig infusion or rapid push). Due to innovation by Ig manufacturers, modern-high percentage Ig preparations can be used to reduce infusion time [57], novel routes (e.g. facilitated s.c. Ig) can be used to give large doses while avoiding a high C_{max} and wear-off effects [58] while standard or rapid-push s.c. Ig offers almost constant plasma concentrations coupled with autonomy and home therapy in countries where this is practised [59,60]. These options give the patient and clinician greater flexibility to optimize patient safety but also satisfaction.

Patient outcome – the need for empirical data

How does the multitude of factors discussed above coalesce in published clinical practice? The effects of obesity on the pharmacokinetics of drugs is contradictory, and even when only protein drugs are considered no consensus can be found within the published literature [61]. Therefore, in order to attempt to understand the role of obesity in dosing immunoglobulin in replacement and immunomodulatory indications we must consider studies which investigate this area specifically. A search of the literature since 2000 revealed six studies of immunoglobulin which considered obese patients specifically or BMI (or approaches which discounted adipose tissue when dosing, e.g. ideal body weight (IBW)).

A UK-based retrospective audit involving 107 CVID patients across four centres did not find any relationship between annual dose and trough level despite normalizing for weight and BMI [62]. The lack of any association may indicate that the sample size and power of this study may have been too small to detect the positive correlation between change in plasma concentration and Ig dose, which has been demonstrated in a number of contemporary studies [52,60,63–65]. Ig studies are at particular risk of this due to the very high interindividual patient variability, which has been documented repeatedly [14,52,56,57,63].

A US study involving 173 PID patients receiving s.c. Ig showed that in both lean and obese patients the increase in serum Ig concentration was proportional to the dose administered and the increase in plasma Ig concentration/g of administered SCIg was the same in both cohorts. These data allowed the author to conclude that there was no difference in the pharmacokinetics of replacement SCIg between obese *versus* lean patients and therefore there was no justification for adjusting the dose in obese patients relative to lean patients [60].

Both these studies considered patients receiving Ig replacement therapy for primary immunodeficiencies, but a significant portion of Ig is now used in high-dose immunomodulation therapy. This distinction is important, not only because of the high volume of Ig use in neurological conditions (43% of the total use in the UK in 2014 [66]), but also because this patient group may be pharmacokinetically distinct, as these patients are largely immunocompetent and generally receive higher doses which lead to higher than physiological IgG plasma concentrations during an extended period [5,52,63,67]. Therefore, data are required for both replacement and immunomodulation dosing regimens.

A smaller study published in 2015 [63] investigated the effect of obesity on dosing for both replacement and autoimmune indications. Although covering a wide dose and plasma concentration range is a positive aspect of this study, it must also come with the caveat that this necessitated the inclusion of patients with different diseases and therefore different pathophysiologies and outcome measures. This was a study in which 31 obese patients were matched with a clinically equivalent lean control at centres where all patients are initiated on an actual body weight dose and then titrated as appropriate based on clinical outcome. This ensured that the minimum dose necessary to optimize the clinical outcome of the patients was administered, and allowed the doses necessary to achieve this to be determined retrospectively. The study found that there was no difference in the obese and lean cohorts at lower replacement doses, but at higher autoimmune doses the obese patients achieved a higher plasma concentration for each gram of Ig administered. This indicated that there is a real pharmacokinetic difference in lean and obese patients at a population level, but only at higher doses. However, the impact on clinical outcome in individuals was not so straightforward. While some obese patients in the cohort benefited from low but clinically effective doses, others required high doses to achieve good outcomes (outcome was measured by number of infections in PID and validated functional scores in the peripheral neuropathy patients). This illustrates that while a pharmacokinetic effect of obesity appears to exist it does not necessarily translate into clinical outcome. This suggests that other patient-specific factors are more important. A study of 15 chronic inflammatory demyelinating polyneuropathy patients whose dose was adjusted to the minimum required to achieve 'best clinical response' found that patients exhibited large interpatient variability in Ig pharmacokinetics but small intrapatient variability [52]. A statistically significant correlation was shown for the relationship between Ig dose and change in IgG plasma

concentration; however, no influence was found when weight and BMI were considered.

One centre reported treating all patients prescribed Ig with an IBW dose over the period a year. Unfortunately, the only outcome reported from this study was the total amount of immunoglobulin diverted from patients and no clinical outcome data were recorded. Although the reduction in dose reduced drug costs, no conclusion can be made on whether the patients experienced positive or negative outcomes as a result [68].

A report of 11 adults, including four who were obese, indicated that the increase in plasma Ig concentration was directly proportional to the actual body weight-adjusted dose [64]. Although no differentiation was made between lean and obese patients in the published work, a personal communication indicated that the obese patients had a larger increase in IgG plasma concentration for the same dose when compared with lean patients. Although this was a very small cohort and unlikely to be statistically significant, it mirrors the data published by Hodkinson *et al.* [63]. No patient outcome data were reported in this study, and the indications were not published, so the potential for insights is limited.

An important gap in all these studies was that they did not report any tolerability or safety-related outcomes, a dose comparison in the same patients (e.g. IBW *versus* standard of care) or a large cohort of obese patients, and therefore the impact of dose in obesity remains unclear. It should be noted that even if such studies did report tolerability data it is unlikely that they would be sufficiently powerful to detect subtle differences in the safety of different dosing strategies.

Implications for clinical practice

There is a balance to be made between the risks of overdosing and underdosing patients (Fig. 2). It is unavoidable that patients will be under- or overdosed if a fixed weight-based dose is applied to Ig, which has such a large interpatient variability [14,52,56,57,63,69,70]. It is essential, therefore, that consideration is given to both clinical and laboratory outcomes to determine whether the delicate balance has been met.

Where doses can be reduced (or the dose interval extended) without compromising efficacy this should be practised, although it should also be taken into consideration that dose titration of immunoglobulin is an inexact science and it is difficult to determine the long-term outcome of any given dosing strategy. There is no validated surrogate measure of long-term benefit for Ig replacement or immunomodulation as can be relied upon when controlling blood sugar in diabetes or when lowering blood pressure to manage cardiovascular risk.

Although questions remain, it has been demonstrated in PID that optimized trough levels of Ig offer a greater level of protection from infection [71–73], and this is key [74] to protect from long-term irreversible damage and therefore also from increased morbidity. Suboptimally dosed patients also cost the health system more in the long term [75]. For these reasons, individual doses should be optimized rationally, not due to short-term cost-saving considerations alone, and kept under regular review, as the patient's circumstances may change over time.

The theoretical complexity of the interactions between dose, efficiacy, interpatient pharmacokinetic variation, safety and cost suggest that a prospective study providing empirical data would be useful to determine the optimal dosing strategy [76]. However, most patient populations which would benefit from immunoglobulin therapy are small, and as differential efficacy would be difficult and lengthy to ascertain such an undertaking is unlikely. A more feasible study would be a prospective pharmacokinetic analysis to determine the relationship between dose, body weight/BMI and clearance. Although such a study would be mechanistically interesting and would solve the core pharmacokinetic question, it would not elucidate the link with patient outcomes in terms of safety and efficacy and therefore would leave open questions.

Although there is no definitive consensus in the published literature regarding the effect obesity has on the dose required, the research taken as a whole suggests that the impact on efficacy is small and unlikely to justify a general dose modification. When this is coupled with the well-documented wide interpatient variability in Ig pharmacokinetics, it is clear that no blanket recommendation can be applied to this population. Although the evidence does not support a blanket dose reduction or cap based solely on obesity, it should be an important consideration for clinicians that obese patients who are being treated for an autoimmune indication may be receiving a large dose while having multiple risk factors.

In summary, clinicians should continue to have the freedom to use their clinical judgement and experience to optimize dosing of Ig on an individual basis for all patients (irrespective of weight). This will ensure that effectiveness is maximized and will reduce the risk of adverse drug reactions which will, in turn, ensure that costs for the health system as a whole in the short and long term are minimized.

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